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PENICILLIN BLOOD LEVELS FOR TWENTY-FOUR HOURS FOLLOWING A SINGLE INTRAMUSCULAR INJECTION OF CALCIUM PENICILLIN IN BEESWAX AND PEANUT OIL*

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IN PREVIOUS reports, we[1-3] have shown that after a single injection of a suspension of calcium penicillin in beeswax and peanut oil, effective levels of penicillin can be maintained in the blood for ten to twelve hours, with excretion continuing in the urine for twenty-four to thirty-two hours. Clinical results[3, 4] have proved as satisfactory by this method of administration as by the method utilizing penicillin in saline solution, which necessitates multiple injections. The preparation most satisfactory for obtaining the above results has proved to be a suspension of 100,000 units of calcium penicillin in 4 per cent beeswax by volume (3.2 per cent by weight) in peanut oil contained in 1 cc. The actual weight of beeswax obtained from a pipette containing 1 cc. is 0.8 gm. Thus, 4 per cent by volume is equivalent to 3.2 per cent by weight.

Our objective has been to prepare a mixture of penicillin that after a single injection will maintain adequate levels of penicillin in the blood for at least twenty-four hours. It was stated in a previous paper[2] that the factor limiting the amount of penicillin that can be suspended in 1 cc. of beeswax and peanut oil is the potency, in Oxford units per milligram, of the penicillin. Early mixtures, which were handshaken, had 30,000 to 50,000 Oxford units of calcium penicillin in beeswax and peanut oil, contained in 1 cc. Since the calcium penicillin averaged 200 to 250 Oxford units per milligram, in terms of amount by weight, the mixture contained approximately 250 mg. in 1 cc.

Subsequently, with the use of a mechanical blender, the particles of penicillin were broken down more finely by agitating the dry powder. The beeswax peanut oil was then added to the powder, and the mixture was blended mechanically. Simultaneously, calcium penicillin assaying at 300 to 500 Oxford units per milligram was available. It was found at this time that the maximum quantity of penicillin powder that could be suspended in beeswax and peanut oil and still be satisfactory from the standpoint of viscosity and prolonged action was approximately 300 mg. contained in 1 cc. This quantity of penicillin displaces about 0.2 cc. of the beeswax and peanut oil in the final suspension. Therefore, in the preparation of the material, 0.8 cc. of beeswax and peanut oil is added, so that the final mixture is contained in a volume of 1 cc. With a potency of 300 to 400 units of calcium penicillin per milligram, satisfactory mixtures of 100,000 units (250 to 300 mg.) of penicillin in 4 per cent beeswax by volume (3.2 per cent by weight) in peanut oil were obtained, with the results shown previously.[3]

It had been hoped that by increasing the volume of a given amount of penicillin per cubic centimeter, a more prolonged effect might be obtained. It was demonstrated, however, that, although 100,000 units in 1 cc. gave a satisfactory assayable level in the blood for an average of seven and a half hours, increasing the total to 3 cc. or 300,000 units resulted in assayable penicillin in the blood for only twelve to fourteen hours. Figure 1 shows the levels of penicillin obtained in the blood after the injection of 100,000, 200,000 and 300,000 units of penicillin in 4 per cent beeswax by volume in peanut oil contained in 1, 2 and 3 cc., respectively. It also shows the duration of excretion of penicillin in the urine with these quantities.

It became obvious that a relatively constant amount of penicillin was being absorbed from each cubic centimeter of the penicillin in beeswax and peanut oil, and by increasing the number of cubic centimeters only slight additional prolongation was achieved, although a marked increase in the height of the level of penicillin in the blood occurred.

When calcium penicillin with a potency of 600 to 800 Oxford units per milligram was obtained, it was possible to suspend 200,000 units of penicillin in 4 per cent beeswax by weight in peanut oil contained in 1 cc. By weight this also represented 250

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Miss Dorothy Talbott, Technician (4th Grade) Mina Levy, Miss Lillian Axelrod and Mrs. Mary Ann Gallagher rendered valuable technical assistance in this study.

to 300 mg. per cubic centimeter of beeswax and peanut oil, and was as satisfactory for use as was the 100,000 units in 3.2 per cent beeswax by weight contained in 1 cc. The more potent mixture produced an assayable level of penicillin in the blood for fourteen to sixteen hours. Increasing the number of cubic centimeters of the mixture caused no prolongation of the level but merely elevated it. When more beeswax was added to the suspension, the penicillin action was not prolonged and the mixture became too viscous for practical use.

As soon as calcium penicillin with a potency of 900 to 1000 units per milligram was available, it was possible to suspend 300,000 units in 4.8 per cent beeswax by weight in peanut oil contained in 1 cc. This mixture, which contains by weight approximately 300 mg. of calcium penicillin per cubic centimeter, is satisfactory from the standpoint of viscosity and maintains adequate levels of penicillin in the blood for about twenty-four hours.

Table 1 shows the results in 50 patients who received a single injection of 300,000 units of calcium penicillin in 4.8 per cent beeswax by weight in peanut oil contained in 1 cc. and had blood assays for penicillin at thirty minutes, and at four-hour intervals for twenty-four hours. Thirty-five of the subjects had a penicillin level in the blood of 0.039 Oxford units per cubic centimeter or higher at the twenty-fourth hour. Seven had this level at the twentieth hour, 5 at the sixteenth, and 3 at the twelfth.

Table 2 shows the results in 37 patients who also had a single injection of 300,000 units, with penicillin assays of the blood either at the twelfth and the twenty-fourth hour or only at the twenty-fourth hour. Twenty-seven subjects had levels of penicillin in the blood of 0.039 Oxford units or higher at the twenty-fourth hour.

More than 50 patients who received a single injection of 300,000 units of penicillin in 1 cc. had daily assays for penicillin in the urine. The average duration of excretion of the drug was three to four days. In addition, 5 patients who also received a single injection of 300,000 units of penicillin in 4.8 per cent beeswax by weight in peanut oil contained in 1 cc. had complete twenty-four-hour specimens of urine collected for five days and had quantitative assays for penicillin determined. Table 3 shows that penicillin was present in their blood for three to four days after the single injection.

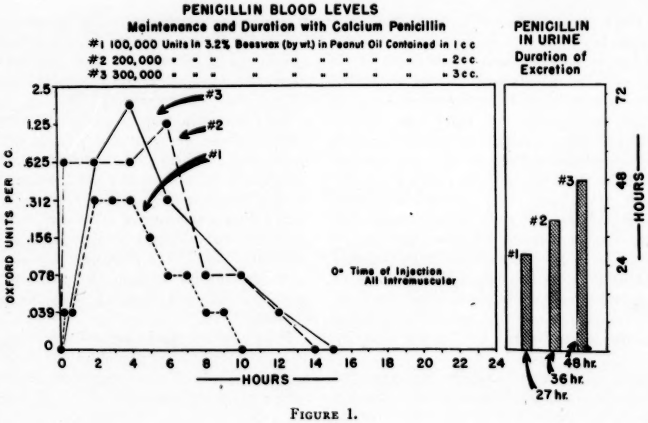

FIGURE 1.

After the first twenty-four hours, it was present in the blood below a level of 0.039 Oxford units, which is the lowest level that can be determined by the methods used.* It was therefore necessary to assay the urine for penicillin. Its presence there for three or four days indicated that it was also in the blood. The reason for the difference in the amount of penicillin recovered from the urine as compared with the amount injected is not apparent at the present time.

Figure 2 shows the levels of penicillin in the blood after single injections of 100,000, 200,000 and 300,000 units of calcium penicillin in 3.2, 4.0 and 4.8 per cent beeswax by weight, respectively, in peanut oil contained in 1 cc., and also the amount and duration of excretion of penicillin in the urine after the injection of these quantities. It is apparent from this figure that a relatively constant absorp-

*Assays of the blood and urine were done by the methods of Rammelkamp[5] and Kirby and Rantz,[6] with minor modifications.

tion of penicillin occurs from 1 cc. of these mixtures. If the concentration is increased in 1 cc., a prolongation of the blood level and excretion results.

As a rule, proportionate amounts of the 300,000 units in 4.8 per cent beeswax by weight in peanut oil contained in 1 cc. will produce and maintain assayable levels in the blood as follows: 0.33 cc. (100,000 units) approximately eight hours; 0.5 cc. (150,000 units) approximately twelve hours; and 0.66 cc. (200,000 units) approximately sixteen hours.

Evidence of a cumulative effect is furnished by the fact that when a single daily dose of 300,000 units in 1 cc. is given for eight days, penicillin continues to be excreted in the urine for approximately six days following the last injection, as compared with three or four days after a single injection of 300,000 units.

A single injection of 2, 3 or 4 cc. of the 300,000 units of calcium penicillin in 4.8 per cent beeswax by weight in peanut oil contained in 1 cc., totaling 600,000, 900,000 or 1,200,000 units, does not, as shown in Figure 3, double, triple or quadruple the

TABLE 1. *Penicillin Blood Levels Produced by a Single Intramuscular Injection of 300,000 Units of Calcium Penicillin in 4.8 Per Cent Beeswax by Weight in Peanut Oil Contained in 1 cc.*

Case No.	Time After Injection							Duration of Assayable Level (0.039 units per cc.)
	½ hr.	4 hr.	8 hr.	12 hr.	16 hr.	20 hr.	24 hr.	
	units/cc.	units/cc.	units/cc.	units/cc.	units/cc.	units/cc.	units/cc.	hr.
1	0.156	0.625	0.625	0.312	0.156	0.078	0.078	24
2	0.312	0.156	0.078	0.156	0.078	0.156	0.156	24
3	0.625	2.50	0.312	0.312	0.156	0.039	0.039	24
4	1.25	1.25	1.25	0.078	0.078	0.078	0.078	24
5	1.25	1.25	0.625	0.625	0.156	0.078	0.078	24
6	0.625	1.25	1.25	0.312	0.078	0.039	0.000	20
7	1.25	1.25	0.312	0.312	0.156	0.078	0.039	24
8	1.25	0.625	0.312	0.312	0.078	0.078	0.078	24
9	2.50	2.50	0.625	0.078	0.039	0.039	0.000	20
10	0.156	0.625	0.312	0.312	0.156	0.156	0.078	24
11	0.312	2.50	2.50	0.312	0.039	0.039	0.039	24
12	0.625	2.50	0.312	0.156	0.078	0.078	0.039	24
13	0.312	0.625	0.312	0.078	0.039	0.000	0.000	16
14	0.625	1.25	1.25	0.156	0.039	0.039	0.078	24
15	0.625	1.25	0.625	0.078	0.000	0.000	0.000	12
16	0.078	0.156	0.078	0.625	0.312	0.078	0.078	24
17	0.312	2.50	1.25	0.078	0.078	0.000	0.000	16
18	0.078	0.078	1.25	0.039	0.039	0.039	0.156	24
19	0.312	0.625	0.625	0.312	0.039	0.039	0.039	24
20	0.156	0.625	0.156	0.156	0.156	0.156	0.312	24
21	0.078	0.078	0.156	0.078	0.000	0.000	0.000	12
22	0.156	0.625	0.312	0.078	0.078	0.078	0.039	24
23	0.625	0.625	0.312	0.156	0.078	0.039	0.039	24
24	2.50	1.25	0.156	0.312	0.156	0.039	0.000	20
25	0.312	1.25	0.156	0.078	0.156	0.078	0.039	24
26	0.312	0.625	1.25	0.156	0.078	0.000	0.000	16
27	0.156	0.625	0.156	0.078	0.078	0.039	0.000	20
28	1.25	1.25	1.25	0.312	0.039	0.000	0.000	16
29	0.156	0.078	0.078	0.078	0.078	0.078	0.039	24
30	0.312	1.25	0.625	0.156	0.078	0.039	0.000	20
31	0.312	1.25	0.625	0.039	0.039	0.078	0.039	24
32	0.312	0.625	0.625	0.078	0.039	0.000	0.000	16
33	0.625	1.25	0.625	0.078	0.000	0.039	0.000	20
34	0.625	1.25	0.625	0.078	0.039	0.078	0.039	24
35	0.312	0.625	0.312	0.156	0.078	0.039	0.078	24
36	0.312	0.625	0.625	0.312	0.039	0.039	0.078	24
37	0.625	0.625	2.50	0.078	0.156	0.078	0.039	24
38	0.156	0.156	0.156	0.156	0.039	0.078	0.078	24
39	0.078	0.156	0.039	0.156	0.039	0.078	0.156	24
40	0.312	1.25	0.625	0.312	0.039	0.039	0.078	24
41	0.312	0.312	0.625	0.625	0.312	0.156	0.078	24
42	0.625	1.25	0.625	0.156	0.078	0.039	0.039	24
43	0.625	0.625	0.625	0.312	0.156	0.039	0.039	24
44	0.156	1.25	0.312	0.312	0.039	0.039	0.156	24
45	0.312	0.625	0.625	0.312	0.156	0.156	0.156	24
46	1.25	1.25	0.312	0.312	0.078	0.039	0.039	24
47	0.625	0.625	0.312	0.312	0.078	0.156	0.078	24
48	2.50	1.25	0.156	0.312	0.156	0.039	0.000	20
49	0.625	1.25	0.625	0.078	0.000	0.000	0.000	12
50	0.625	1.25	0.625	0.078	0.039	0.078	0.039	24

time for which assayable levels are present in the blood. It does, however, produce extremely high levels. Figure 3 also shows the amount and duration of excretion of penicillin in the urine after the injection of these quantities.

TABLE 2. *Penicillin Blood Levels Produced at 12 and 24 Hours after a Single Intramuscular Injection of 300,000 Units of Calcium Penicillin in 4.8 Per Cent Beeswax by Weight in Peanut Oil Contained in 1 cc.*

Case No.	Time After Injection 12 hr.	24 hr.	Duration of Assayable Level (0.039 units per cc.)
	units/cc.	*units/cc.*	*hr.*
51	0.312	0.039	24
52	0.312	0.156	24
53	— *	0.625	24
54	0.625	0.000	12
55	0.625	0.078	24
56	0.078	0.156	24
57	0.156	0.039	24
58	—	0.000	?
59	—	0.000	?
60	—	0.156	24
61	—	0.078	24
62	—	0.078	24
63	—	0.156	24
64	—	0.039	24
65	—	0.039	24
66	—	0.039	24
67	—	0.039	24
68	0.625	0.078	24
69	—	0.312	24
70	—	0.000	?
71	—	0.078	24
72	0.312	0.000	12
73	—	0.156	24
74	—	0.078	24
75	—	0.000	?
76	—	0.039	24
77	—	0.156	24
78	—	0.156	24
79	0.312	0.000	12
80	—	0.039	24
81	0.156	0.000	12
82	0.625	0.000	12
83	—	0.312	24
84	—	0.078	24
85	—	0.039	24
86	0.312	0.039	24
87	0.078	0.000	12

*Blood not withdrawn for penicillin assay.

to suspend 495,000 units in 1 cc. of beeswax and peanut oil. This quantity would be equivalent in weight of penicillin to 300 mg. One cubic centimeter of this mixture would theoretically produce adequate levels in the blood for somewhat over thirty-six hours.

This and the data previously presented[1–3] suggest that the mechanism that causes the prolonged action of penicillin when suspended in beeswax and peanut oil is due to the following fact. Beeswax and peanut oil when heated sufficiently yield a clear liquid, but when the mixture reaches approximately 37°C. it becomes opaque, indicating that the beeswax is forming small particles. In preparing the penicillin in beeswax and peanut oil[3] it is the clear liquid that is added to the penicillin powder and blended until a complete suspension occurs. When this final mixture cools to room temperature or 37°C., numerous minute particles of beeswax interspersed with minute granules of penicillin can be observed under the microscope. This indicates that when

TABLE 3. *Amount and Duration of Excretion of Penicillin in the Urine after a Single Injection of 300,000 Units of Calcium Penicillin in 4.8 Per Cent Beeswax by Weight in Peanut Oil Contained in 1 cc.*

Case No.	Time After Injection 24 hr.	48 hr.	72 hr.	96 hr.	120 hr.	Total Excretion
	units	*units*	*units*	*units*	*units*	*units*
47	151,135	6,500	940	0	0	158,575
50	136,105	29,300	1,031	198	0	166,635
81	154,000	7,370	1,360	27	0	162,757
82	179,000	975	244	85	0	180,304
87	116,000	10,300	1,340	195	0	127,835
Averages	147,248	10,889	983	101	0	159,221

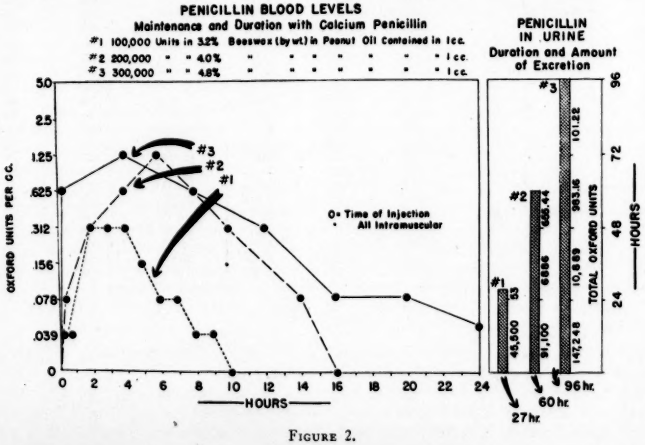

FIGURE 2.

If crystalline penicillin assaying at 1650 units per milligram were available, it should be possible

the penicillin in beeswax and peanut oil is injected intramuscularly at a temperature of 37°C., the particles of beeswax retard its absorption.

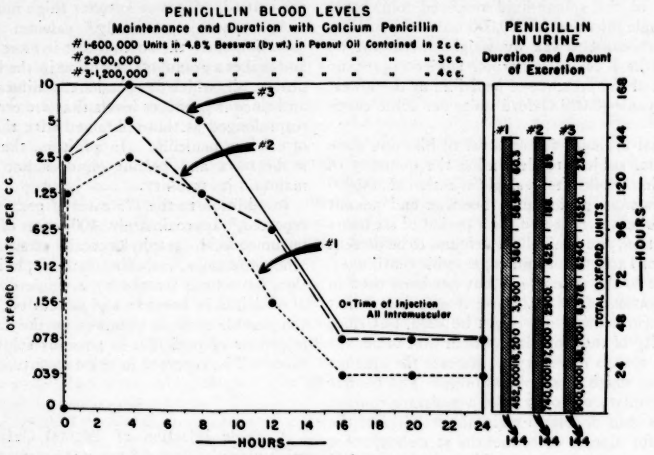
PENICILLIN BLOOD LEVELS
Maintenance and Duration with Calcium Penicillin
#1-600,000 Units in 4.8% Beeswax (by wt) in Peanut Oil Contained in 2 c.c.
#2-900,000 " " " " " " " " " 3 c.c.
#3-1,200,000 " " " " " " " " " 4 c.c.
PENICILLIN IN URINE
Duration and Amount of Excretion
OXFORD UNITS PER C.C.
HOURS
TOTAL OXFORD UNITS
#1
#2
#3
O=Time of Injection All Intramuscular

FIGURE 3.

DISCUSSION

In view of the above and previous data, the following might be used as a basis of therapy. A single daily dose of 300,000 units in 4.8 per cent beeswax by weight in peanut oil contained in 1 cc. should be adequate for all but overwhelming infections. It seems logical that the dose of penicillin should be the amount that will maintain adequate levels of penicillin in the blood for twenty-four hours, rather than different quantities for each disease. Patients whose weight is 100 pounds or less can be given 2000 units per pound and will maintain adequate penicillin levels in the blood

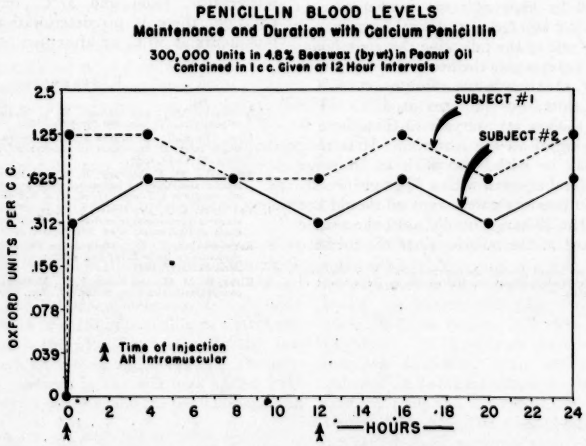
PENICILLIN BLOOD LEVELS
Maintenance and Duration with Calcium Penicillin
300,000 Units in 4.8% Beeswax (by wt) in Peanut Oil
Contained in 1 c.c. Given at 12 Hour Intervals
OXFORD UNITS PER C.C.
HOURS
SUBJECT #1
SUBJECT #2
Time of Injection
All Intramuscular

FIGURE 4.

for twenty-four hours. For extremely severe infections, 300,000 units in 1 cc. can be given at twelve-hour intervals, producing penicillin levels in the blood as shown in Figure 4.

Studies of the spinal fluid removed four hours after a single injection of 300,000 units of penicillin in 4.8 per cent beeswax by weight in peanut oil contained in 1 cc. in 6 normal subjects gave no indication of the presence of penicillin at the lowest level assayable (0.039 Oxford units per cubic centimeter).

Duodenal drainage for removal of bile was done in 1 normal subject to determine the quantity of penicillin in the bile after a single injection of 300,000 units of calcium penicillin in beeswax and peanut oil. The bile was collected for a period of six hours after injection, and penicillin was found to be present at a level of 1 to 2 Oxford units per cubic centimeter.

Relative to the type of oil that has been used in the preparation of this mixture, it was found that sesame, corn or other oils might be used, but since the viscosity of these oils is less than that of peanut oil, it was always necessary to increase the amount of beeswax, which was not desirable. The peanut oil* in the mixture should have a moisture content of 0.05 per cent or less to maintain stability of the penicillin for nine or more months at icebox, room and 37°C. temperatures. In addition, no deterioration of the calcium penicillin in beeswax and peanut oil occurs for twenty-four to thirty-six hours at 56°C. or for two hours at 100°C. Details of the stability of the penicillin in this mixture will be reported soon.

The above data on stability indicate that the material should be kept at room temperature — except during long storage — and may be prepared for injection by one of the following three methods: three to five minutes under the hot-water tap (56 to 60°C.); twenty to twenty-five minutes at 45°C.; and thirty to thirty-five minutes at 37°C. The preparation is shaken at intervals so that there is thorough warming of all the material. After this, the mixture may be withdrawn with an 18-gauge or larger needle and injected with a 20-gauge needle. The penicillin in beeswax and peanut oil should not be forced into the 20-gauge needle until the needle has been inserted in the muscle, since the mixture occasionally hardens in the metal needle, making it difficult to inject. A dry syringe and needle should *always* be used. Injections may be given in the upper outer quadrant of the buttock or in the deltoid, triceps or anterior thigh muscles.

As reported previously,[3] calcium penicillin is essential, since the sodium salt is more hygroscopic and makes a granular suspension in the beeswax and peanut oil, which is occasionally difficult to inject, and since it produces levels that are erratic and not so prolonged as those obtained with the suspension of calcium penicillin. In addition, the sodium salt in beeswax and peanut oil does not consistently maintain its stability.

In addition to the 175 cases of gonorrhea already reported,[3] approximately 400 cases of gonococcal, pneumococcal, staphylococcal, streptococcal and other infections, including early syphilis and impetigo, have been treated by a single daily injection of penicillin in beeswax and peanut oil, with results comparable to those obtained by the daily multiple injections of penicillin in aqueous solution. These cases will be reported in the near future.

*This peanut oil was obtained through the courtesy of Dr. K. S. Markley, Southern Regional Research Laboratory, United States Department of Agriculture, New Orleans.

Summary

A single injection of 300,000 Oxford units of calcium penicillin in 4.8 per cent beeswax (by weight) in peanut oil contained in 1 cc. produces and maintains effective levels of penicillin in the blood for about twenty-four hours, and continues to be excreted in the urine for approximately three days.

Calcium penicillin in beeswax and peanut oil maintains its potency for at least nine months at refrigerator, room and 37°C. temperatures. In addition, there is no deterioration after twenty-four hours at 56°C. or after two hours at 100°C.

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THE TREATMENT OF GONOCOCCAL URETHRITIS WITH SINGLE INJECTIONS OF PENICILLIN-BEESWAX-PEANUT OIL MIXTURES*

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ROMANSKY and Rittman[1, 2] have developed a practical and apparently safe procedure for retarding the absorption of penicillin by suspending it in a mixture of peanut oil and beeswax, and have reported favorable results in the treatment of gonococcal urethritis.

During the last nine months, various mixtures of penicillin in beeswax and peanut oil have been prepared and investigated at this hospital in an attempt to determine which one would produce the most satisfactory results, from the standpoint both of prolongation of blood levels and of clinical results. In the course of these studies, 217 men with acute gonococcal urethritis were treated with single intramuscular injections of one of these preparations. One hundred and forty-five patients were hospitalized for two days for the collection of blood and urine specimens, but were ambulatory. The remainder were treated as outpatients.

The patients had untreated, uncomplicated gonococcal urethritis, with the following exceptions: 4 had failed to respond to 100,000 units of penicillin in saline solution, given in four intramuscular injections of 25,000 units at three-hour intervals; 1 had failed after two such courses; 10 had failed after sulfonamide therapy; and 3 had epididymitis as well as urethritis.

All the patients had the characteristic clinical picture of acute gonococcal urethritis, with purulent urethral discharge, and the diagnosis was confirmed by smears and cultures. Following the single intramuscular injection of a penicillin-beeswax-peanut oil mixture, each patient was restricted to his military area for a period of twenty-one days, to obviate the possibility of reinfection. Post-treatment observations, consisting of a careful clinical examination, smear and culture of any urethral discharge and culture of the centrifuged urine sediment, were made on the second, seventh, fourteenth and twenty-first days.

The penicillin-beeswax-peanut oil mixtures were prepared in our own laboratory by mixing appropriate amounts of preheated, sterile, highly refined peanut oil† and bleached beeswax *U.S.P.* with powdered sodium or calcium penicillin in a mechanical blender until the penicillin was uniformly suspended throughout the oil and beeswax. The concentration of beeswax in the mixtures varied from 4 to 12 per cent by volume, and the penicillin content from 100,000 to 300,000 units per cubic centimeter. The procedure and materials used were essentially the same as those described by Romansky and Rittman[2] and need not be repeated in detail. Similarly, the technic of injection requires no elaboration. It should be pointed out, however, that when 300,000 units of penicillin are suspended in 4 per cent beeswax, or when 100,000 units are suspended in 10 or 12 per cent beeswax, in a total volume of 1.0 cc., the mixtures are extremely viscid, even after being heated in an incubator or in a water bath at 37°C. for thirty minutes. A 15-gauge needle was used to withdraw the mixtures into a syringe, and although considerable pressure on the plunger was required the material was injected into the buttock through a 20-gauge needle. The site of the injection was not massaged.

Assays of the blood and urine, which were performed in most of the cases, are briefly summarized later in this paper, and will be separately reported in detail.

No significant local or systemic manifestations of toxicity were noted following administration of the penicillin-beeswax-peanut oil mixtures. In most cases pain and tenderness were present at the site of injection for twenty-four to forty-eight hours, but these were no severer than when penicillin in saline solution is used.

Following the injection, clinical improvement was noted initially in all the 217 patients treated. Dysuria subsided during the first six to eight hours, and the purulent discharge became mucoid and watery. By the end of the second day almost every patient was free of symptoms and the urethral discharge had ceased. In general, the rapidity of clinical improvement was similar to that seen with penicillin in saline solution.

Of the 217 patients treated, 10 were followed for only seven days and 15 for only fourteen days, and none had clinical or bacteriologic evidence of relapse during that time, but since these patients did not fulfill the basic criterion of a twenty-one-day follow-up period, only the remaining 192, which were followed for twenty-one days, were considered in evaluating the results. Of these, 24 were failures (Table 1). In 10 patients there was a recurrence of urethral discharge, from which gonococci were cultured; in 8 of these relapse occurred by the seventh day, in 1 on the fourteenth day and in 1 on the twenty-first day. The other 14 failures were detected by bacteriologic methods alone — 7 on the seventh day, 3 on the fourteenth day, 1 each on the tenth and twelfth days and 2 on the twenty-first day.

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†The specially refined peanut oil was kindly supplied by the Southern Regional Research Laboratory, United States Department of Agriculture, New Orleans.

The relation of the total dose of penicillin to the percentage of cures is presented in Table 2. Of 88 patients treated with 100,000 units, 74 (84 per cent) were cured, and of 91 treated with 300,000 units, 83 (91 per cent) were cured. With 200,000 units, 11 of 13 patients were cured, but the numbers were too small to be significant.

In Table 3 the data are further subdivided to show the results in relation to the concentrations of beeswax present in the various mixtures and to the salt of penicillin employed (sodium or calcium). In this group of cases sodium penicillin gave results equally satisfactory to those obtained with calcium penicillin, from the standpoint both of prolongation of blood levels and of therapeutic result. The total number of units of penicillin in any given mixture was of much more importance in determining the results, from both the clinical and the laboratory standpoint, than was the salt of penicillin used.

TABLE 1. *Cases of Failure Classified according to the Day after Treatment that Failure Was Detected.*

Criteria for Diagnosis of Failure	No. of Cases	Day after Treatment that Failure Was Detected						
		2	3	7	10	12	14	21
Clinical and bacteriologic	10	3	2	3	0	0	1	1
Bacteriologic only	14	0	0	7	1	1	3	2
Totals	24	3	2	10	1	1	4	3

TABLE 2. *Therapeutic Results in 192 Patients Observed for a Minimal Period of 21 Days and Classified according to Dose of Penicillin Administered.*

Dose of Penicillin	No. of Cases	Success		Failure	
		No.	Percentage	No.	Percentage
units					
100,000	88	74	84	14	16
200,000	13	11	85	2	15
300,000	91	83	91	8	9
Totals	192	168		24	

TABLE 3. *Therapeutic Results Obtained with Various Penicillin Beeswax-Peanut Oil Mixtures in 217 Patients.*

Content of Beeswax*	Salt of Penicillin	Dose of Penicillin	No. of Cases	Success		Failure
				followed less than 21 days	followed 21 days or more	
%		units				
4	Calcium	100,000	81	3	67	11
4	Calcium	200,000	8	0	7	1
4	Calcium	300,000	15	4	10	1
5	Sodium	300,000	9	1	8	0
5	Calcium	300,000	9	2	7	0
6	Sodium	100,000	5	2	1	2
6	Sodium	300,000	7	3	4	0
8	Sodium	100,000	4	0	4	0
8	Sodium	200,000	7	2	4	1
8	Sodium	300,000	34	3	29	2
8	Calcium	100,000	3	0	2	1
8	Calcium	300,000	13	3	9	1
10	Sodium	300,000	6	0	5	1
12	Sodium	300,000	10	2	8	0
12	Calcium	300,000	6	0	3	3
Totals			217	25	168	24

*By volume.

All the 24 patients who were failures were eventually cured by further penicillin-beeswax-peanut oil therapy or by treatment with divided doses of penicillin in saline solution.

Of the 192 patients evaluated, 96 were Whites and 96 Negroes, with approximately equal racial distribution in the three penicillin-dosage groups. There were 10 failures (10 per cent) among the Negroes and 14 failures (15 per cent) among the Whites. This greater refractoriness of gonococcal urethritis in the latter, which has been noted many times with both the sulfonamide drugs and penicillin, is a factor to be considered in evaluating the results of therapy.

Discussion

The observation of Romansky, Murphy, and Rittman[3] that a single intramuscular injection of a penicillin-beeswax-peanut oil mixture is a highly effective method of treating acute gonococcal urethritis has been confirmed by the present studies. The results can be best evaluated by comparing them with those obtained with single or multiple injections of penicillin in saline solution. Of 100 men treated at this hospital with a single intramuscular injection of 100,000 units of penicillin in saline solution and followed both clinically and bacteriologically for a period of twenty-one days, 74 per cent were cured,[4] as compared with the 84 per cent cured in the present series with a single injection of 100,000 units of penicillin in beeswax-peanut oil. The treatment of 600 men with 100,000 units of penicillin in saline solution in divided doses by several different time schedules resulted in 90 to 93 per cent cures,[4] which compares favorably with the 91 per cent cures obtained in the present series with a single injection of 300,000 units of penicillin in beeswax-peanut oil. Thus, it appears that larger amounts of penicillin are required in single injections of the mixtures to produce results equivalent to those obtained with multiple injections of penicillin in saline solution.

Romansky, Murphy and Rittman reported 93 per cent cures of 100 patients treated with a single dose of 100,000 units and 100 per cent cures of 75 patients treated with a single dose of 150,000 units of a penicillin-beeswax-peanut oil mixture. Since the mixtures used by them were not identical with those of the present series, and since their cases were followed bacteriologically for only seven days, the results are not strictly comparable. Of the relapses in 24 cases in the present series, 9 occurred subsequent to the seventh day, and in these 7 patients failed to develop symptoms, the relapse having been detected by bacteriologic methods alone. The importance of a clinical and bacteriologic follow-up period of a minimum of twenty-one days, which is apparent from these observations, has also been emphasized by others. Recently, Lapenta, Weckstein and Sarnoff,[5] using penicillin in saline solution, detected bacteriologic relapses up to nineteen days

following therapy, and concluded that, for proper evaluation of the results of treatment, cultures should be made at intervals for at least twenty-one days.

Under the auspices of the United States Public Health Service,[6] 1060 patients, both male and female, with gonococcal urethritis or endocervicitis have recently been treated by single intramuscular injections of 200,000 units of penicillin in beeswax-peanut oil, with 91 per cent cures. These results are equivalent to those obtained with 300,000 units in the present series. The minimum standard for cure in the United States Public Health Service cases was a post-treatment observation period of at least ten days, with at least three negative cultures, including one on the tenth day of observation.

Assays of penicillin in the blood and urine were performed in most of the cases included in the present series and will be reported separately in detail. The information obtained from these assays clarified the clinical results. There was a striking variability of absorption and excretion with all the mixtures employed. With 100,000 units, assayable levels* were present in the blood stream for zero to sixteen hours, with the majority falling between four and eight hours. In a good many cases, levels could be detected for only four hours or less, a duration not significantly longer than that obtained with penicillin in saline solution, and sometimes not so long. Similar variability was observed when the mixtures contained 300,000 units of penicillin: assayable levels persisted for four to twenty-eight hours, and in most cases such a level was present for eight hours or more. This is roughly equivalent to the total duration of assayable levels obtained with 100,000 units of penicillin in saline solution when given in four intramuscular injections of 25,000 units each at three-hour intervals — that is, an assayable level for approximately two hours following each injection. There is apparently a relation between the duration of assayable penicillin in the blood and the clinical results. Thus, the results with 100,000 units of penicillin in saline solution, given in divided doses, were superior to those with 100,000 units of penicillin in beeswax-peanut oil, but were approximately equal to those with 300,000 units of penicillin-beeswax-peanut oil.

From the present studies, which included clinical and laboratory observations made with a variety of preparations, it appears that the penicillin-beeswax-peanut oil mixture used for the single-dose treatment of gonococcal urethritis should contain 200,000 or 300,000 units of penicillin, preferably the latter. Contrary to the impression of others, experience in this laboratory indicates that, from the standpoint both of prolongation of blood levels and of clinical results, sodium penicillin is as satisfactory as the calcium salt. Since concentrations of beeswax varying from 4 to 12 per cent produced closely similar results, 4 to 6 per cent (by volume) in a total volume of 1.0 cc. is recommended because such mixtures are less viscid and also contain less of the foreign material (beeswax). Preparations meeting these requirements — that is, 300,000 units of penicillin in 1.0 cc. of a mixture of 4.8 per cent of beeswax by weight in peanut oil — are now being made for experimental study by several commercial houses, and one such preparation is under investigation in this laboratory at the present time. A report of the laboratory and clinical results with this material will be published elsewhere.

The two chief disadvantages of the beeswax-peanut oil mixtures are the larger amounts of penicillin required and the difficulty in heating and handling the viscid material. These disadvantages are, however, more than offset by the convenience of curing patients with a single intramuscular injection. Penicillin-beeswax-peanut oil mixtures offer the simplest and most practical method for the treatment of acute gonococcal urethritis in the office and the outpatient clinic. They may be useful in the treatment of diseases requiring prolonged and repeated injections of penicillin.

*The Kirby-Rantz[7] modification of the Rammelkamp assay method was used, and the minimal assayable level, by this method, is 0.04 Oxford units of penicillin per cubic centimeter.

Summary

Two hundred and seventeen men with gonococcal urethritis were treated with single intramuscular injections of 100,000 to 300,000 units of penicillin suspended in mixtures of beeswax and peanut oil. No local or systemic toxic manifestations were noted.

Of 88 patients treated with single injections of 100,000 units, 74 (84 per cent) were cured, and of 91 treated with 300,000 units, 83 (91 per cent) were cured. The results with 300,000 units of penicillin in beeswax-peanut oil were comparable with those obtained with 100,000 units of penicillin in saline solution given in divided doses; in other words, to produce equal results the mixtures required larger amounts of penicillin than did the saline solution.

All patients were followed for a minimum of twenty-one days, both clinically and bacteriologically. Of the failures in 24 cases, those in 9 occurred subsequent to the seventh day, and of these 7 were detected by bacteriologic methods alone. These results stress the necessity for a minimal post-treatment observation period of twenty-one days.

Assays of the blood and urine showed marked variability of absorption and excretion of penicillin following injections of the mixtures.

Sodium and calcium penicillin produced equally satisfactory mixtures, from both the clinical and the laboratory standpoint. Varying the concentration of beeswax from 4 to 12 per cent did not produce a significant difference in the results.

A single intramuscular injection of 1.0 cc. of a mixture containing 300,000 units of penicillin in 4 to 6 per cent beeswax by volume in peanut oil appears to be a highly satisfactory method of treating acute gonococcal urethritis.

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SURGICAL RELIEF FOR TRACHEAL OBSTRUCTION FROM A VASCULAR RING*

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IN 1931, I performed an autopsy on a five-month-old baby who had had wheezing respirations since birth and had recently developed difficulty in swallowing. At this examination a ring of blood vessels was found encircling the intrathoracic portion of the esophagus and trachea in such a way that the esophagus was indented from behind, whereas the trachea was compressed on its anterior surface. The pathological findings at once suggested that a division of some part of the so-called "vascular ring" during life would probably have relieved the pressure on the constricted esophagus and trachea.

The above-mentioned case aroused my curiosity, and a rather extensive investigation of the literature has shown that quite a few examples of vascular ring have been found and described by various authors. Many of the observations have been made on aged adults receiving anatomical-room dissection, there having been no apparent symptoms during life. Conversely, some of the malformations have been uncovered in infants or children known to have had serious obstruction of the esophagus or trachea. The impression is gained that the majority of these vascular abnormalities give little or no symptomatology and are only incidentally discovered at post-mortem examination, but that in occasional cases the ring produces important complaints at an early age and indeed may lead to a fatal issue. Apparently, a vascular ring of large size is unlikely to give rise to symptoms, but in patients with a circle of relatively small size there are signs of esophageal and especially tracheal compression.

Vascular rings within the mediastinum are of two general types. In the first, the aortic arch is missing from its normal position in front of the trachea, and instead courses behind the esophagus. The pulmonary artery lies in a normal position in front of the trachea, but it is anchored to the distal part of the aortic arch by a patent ductus arteriosus — or a ligamentum arteriosum — at the left side of the esophagus and trachea. Hence, the esophagus is compressed from behind by the aortic arch and the trachea is encroached on anteriorly by the pulmonary artery. It is conceivable that division of the patent ductus arteriosus or the ligamentum arteriosum would allow the pulmonary artery to fall forward and give sufficient room for the esophagus and trachea. The second general type of vascular ring is in effect a divided or split aortic arch. At a short distance above its valve, the aorta divides into two limbs. One of these passes posteriorly and then to the left behind the esophagus, and the other courses to the left in front of the trachea, the two merging in the left side of the mediastinum and forming the descending aorta. The innominate artery, the left common carotid artery and the left subclavian artery may all come from the anterior limb or from the posterior limb. More often, both limbs give rise to these various arteries. The limbs may be of approximately the same diameter, but one is apt to be larger than the other. A study of the previously recorded cases makes it obvious that the anatomic arrangements are frequently of a sort that make it impossible to divide any part of the ring without disturbing important vascular pathways. In other cases, however, it is certain that some part of the ring could be cut safely and that this would permit spreading of the ring to a degree that would relieve constriction of the esophagus and trachea.

In the following case, both types of vascular ring were present. First, the pulmonary artery was held tightly in a posteriorly displaced position by the ligamentum arteriosum, the division of which allowed the pulmonary artery to sag forward. Second, there was a split aortic arch, and division of its anterior limb immediately took considerable pressure off the anterior and left lateral surfaces of the trachea. So far as I know, this is the first patient for whom surgical division of a vascular ring has ever been attempted.

Case Report

A 4-month-old infant was admitted on October 14, 1944, with a chief complaint of wheezing respirations since birth. Because of a widened superior mediastinal shadow, which was thought to represent an enlarged thymus, x-ray therapy was given. The patient was discharged on October 23, but was readmitted on November 13. There had been no improvement in the respiratory difficulty following the irradi-

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ation. For the last 24 hours there had been a cough, increasing distress during breathing efforts, fever, noisy respirations and a bout of vomiting.

Examination showed a seriously ill baby with extremely labored respirations. There was moderate intercostal retraction. Many coarse rhonchi were heard over both lung fields. The temperature was 101°F., and the white-cell count 12,800. The patient was thought to be suffering from an acute tracheobronchitis, and was placed in a steam room and given sulfadiazine. The fever gradually subsided to normal in 10 days. Five days later he appeared to be in fairly good condition and no longer showed intercostal retraction. However, noisy respirations and an intermittent cough continued throughout the hospital stay. He was discharged on December 2.

The patient was admitted for the third time on March 16, 1945. For 3 days there had been increasing wheezing, cough, dyspnea and fever. The cry had become hoarse. Coughing had greatly interfered with feeding and with sleeping. At times the breathing was quite labored.

Examination showed the patient to be in moderate respiratory distress. The temperature was 102°F., and the respirations 55. The mucous membranes of the throat were injected. There was moderate intercostal and suprasternal respiratory retraction. Throughout both lung fields were diffuse rales, which were particularly coarse during expiratory phases. The white-cell count was 18,700. A throat culture grew out moderate numbers of beta-hemolytic streptococcus and *Staphylococcus aureus*. Fluoroscopy showed an increased density in the region of the right middle lobe. Through the remainder of the chest there was a rather diffuse and patchy pneumonic infiltration.

The patient was immediately placed in a steam room, and sulfadiazine, as well as intramuscular penicillin, was started. During the first 24 hours his condition became distinctly worse. The temperature rose to 104.2°F., the respirations were much more labored, and cyanosis appeared. An oxygen tent gave some relief, but on the 3rd day the temperature again spiked to 104°F. Subsequently conditions improved; the temperature gradually subsided, the respirations became less labored, and the general appearance of the patient was less alarming. By the 7th day he had recovered sufficiently to be taken out of the steam room, and the penicillin was discontinued. Sulfadiazine was used until the 12th day. On the 11th day, a second roentgenologic examination of the chest showed widespread improvement of the lung, but the right middle lobe was still partially atelectatic. On April 3, bronchoscopy was performed and the orifice of the right middle lobe was found to be inflamed and possibly narrowed. On April 6, the patient was discharged in a fairly satisfactory state.

The fourth admission was on May 24, 1945. Since the previous discharge there had been persistent wheezing respirations, which, however, did not appear to interfere appreciably with the patient's health. For 4 days there had been increasingly severe cough and aggravation of the chest wheezing. The respirations had become extremely noisy, and saliva often accumulated in the throat and blocked the airway.

Examination revealed a well developed and well nourished infant in acute respiratory distress. He was breathing with great difficulty. There was moderate retraction of the suprasternal and intercostal spaces. The breath sounds were noisy and crowing. There were many coarse rhonchi throughout both lung fields. The temperature was 103°F., the white-cell count 12,250, and the red-cell count 3,480,000.

Immediately after admission to the ward the patient became quite cyanotic and was in collapse for a few hours. He was placed in an oxygen tent, and intramuscular penicillin was started. On the 2nd day, the respiratory signs were about the same, although the dyspnea had slightly decreased and the color was greatly improved. On the 3rd day the dyspnea had further diminished, the fever had disappeared, and the patient's general status was much better. By the end of a week he had almost completely recovered from the tracheobronchitis. There was still, however, a prominent wheezing sound during inspiration. This was especially noticeable during and after eating and was more audible when the respiratory efforts were increased by exercise and crying.

In an effort to detect some underlying abnormality that might have made the patient susceptible to repeated attacks of tracheitis, several investigations were undertaken. Roentgenologic study revealed the following (Fig. 1). Visualization of the esophagus in the anteroposterior view after a swallow of barium showed it to be very slightly narrowed opposite to the 3rd or 4th thoracic vertebra. At this level, the lateral view indicated a marked indentation of the posterior wall of the esophagus and a forward displacement of the esophagus. A mass appeared to lie between the esophagus and the vertebral column. Visualization of the trachea and

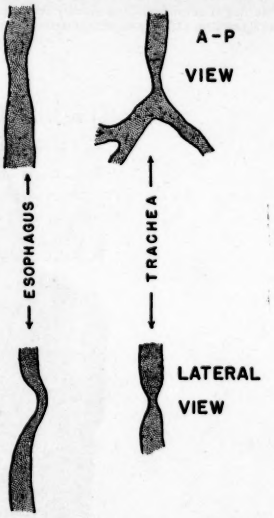

FIGURE 1. *Tracings Made from Preoperative Roentgenograms (barium in the esophagus and lipiodol in the trachea).*
In the anteroposterior view there is little narrowing of the esophagus but there is a definite narrowing of the trachea just above its bifurcation. In the lateral view the esophagus has a marked indentation on its posterior wall and the trachea has a distinct constriction.

bronchi after instillation of lipiodol showed a fairly marked narrowing of the trachea just above its bifurcation and at the general level corresponding with the previously described esophageal deformity. This narrowing was present in the anteroposterior view and was particularly prominent in the lateral film. There was no definite abnormality of the remaining portions of the tracheal or bronchial tree. Lipiodol freely entered the right middle lobe. These findings in the esophagus and trachea were interpreted by Dr. Edward Neuhauser as indicating the presence of a vascular ring.

Shortly after completion of the above studies, there was a sudden and severe flareup of the respiratory troubles. The respiratory rate rose, the pulse increased rapidly, and fever appeared. On the following day the respirations had reached 60, the pulse 160, and the temperature 103°F. At that time inspiratory and expiratory stridor was marked and there was intercostal and suprasternal retraction, as well as mild to moderate cyanosis. Sulfadiazine and penicillin were started.

Operation was performed on June 9. Although it might have been preferable to wait until all evidence of respiratory infection had disappeared, it was believed that the patient would have a better chance of combating the tracheitis if the trachea could be relieved of its mechanical obstruction. Operation was therefore proceeded with, in spite of the precarious state of the patient. Under cyclopropane anesthesia

the chest was opened through a left anterolateral incision, with entrance to the pleural cavity through the third interspace and division of the 3rd and 2nd costal cartilages. The left pleural cavity was traversed to reach the mediastinal structures. Opening of the mediastinal pleura and subsequent dissection of tissues gave an excellent view of the great vessels, all of which could be identified with certainty. A short distance above its origin, the ascending aorta divided into two limbs, which coursed upward to the left and joined to form the descending aorta (Fig. 2). This divided arch formed a ring that enclosed and greatly constricted the esophagus and trachea. The innominate artery, the left common carotid artery and the left subclavian artery arose as indicated in the illustration. The pulmonary artery seemed to be held tightly against the anterior surface of the trachea by its attachment — through the ligamentum arteriosum — to the aorta.

After all the above anatomic findings and variations had been carefully identified, steps were taken to relieve the tracheal compression. First, the ligamentum arteriosum was divided between silk ligatures to allow the pulmonary artery to fall forward and away from the trachea. This had some slight beneficial effect on the respiratory exchange, but it was not marked. It was then decided to divide some portion of the arterial ring that encircled the esophagus and trachea. If the posterior branch of the split aortic arch had been smaller than the anterior one, I should have preferred to cut it, since this would have more nearly returned the vascular system to a normal arrangement. However, since the posterior branch was the larger of the two limbs, it was believed that division of the anterior one would give less interference to the supply of blood to the descending aorta. The anterior aortic arch was severed as indicated in Figure 3. When this was done, the left common carotid artery immediately displaced superiorly and toward the right and the trachea was obviously relieved of most of the existing compression. During the first part of the operation the respiratory distress caused extreme anxiety; there was a loud and prominent inspiratory and expiratory crow, and the pronounced shift in the mediastinum with each of the respiratory movements made the dissection quite difficult. As soon as the anterior aortic arch had been divided, however, the respirations quieted down, most of the crowing disappeared, and the respiratory shift in the mediastinum diminished to a normal degree. The chest wall was closed in an appropriate manner, the left lung being completely expanded before final repair of the wound.

To combat the residual tracheal infection, the patient was

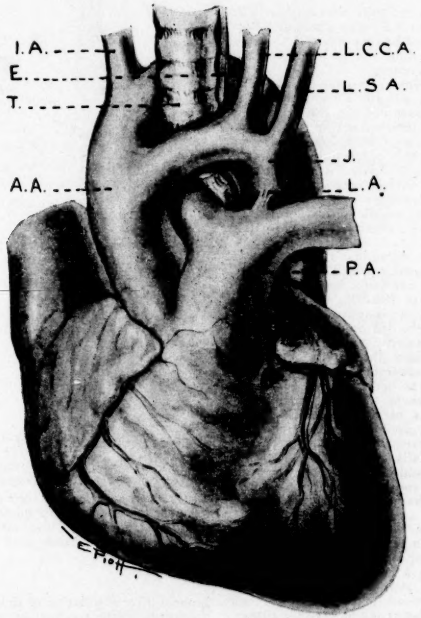

FIGURE 2. *Arrangements of the Great Vessels as Found at Operation. The ascending aorta bifurcates into two branches; one passes behind the esophagus, and the other arches in front of the trachea. The two branches join to form the descending aorta. Within the vascular ring the esophagus and trachea are compressed.* AA — *ascending aorta;* E — *esophagus;* IA — *innominate artery;* J — *junction of the two aortic arches;* LA — *ligamentum arteriosum;* LCCA — *left common carotid artery;* LSA — *left subclavian artery;* PA — *pulmonary artery, and* T — *trachea.*

placed in a steam room for 1 week and was given parenteral sulfadiazine and penicillin for 16 days. By the 5th postoperative day, the fever had gradually disappeared, the pulse had slowed to a normal rate, and the respirations had fallen to 25 or 30. The wound healed per primam. After 1 week, the acute stage of the tracheal infection had disappeared and the respiratory system appeared to become stabilized. The effects of the operation could then be evaluated. The patient was alert and playful and had no distress of any kind. With the ear held close to the chest a faint inspiratory sound could be heard. During and immediately following deglutition of food these inspiratory sounds became slightly louder — apparently because the esophagus was still displaced forward by the aortic arch behind it and was causing some pressure on the posterior wall of the trachea.

On July 7, roentgenographic examinations were again performed to visualize the esophagus and trachea. There was no change in the esophagus from its preoperative state. The trachea still presented some narrowing above its bifurcation, but this was distinctly less marked than it had been before operation. Although there was some indentation along the right side of the trachea, the left border had straightened out considerably following the operative procedure. The deformity that remains in the trachea may be due to some residual pressure from the left common carotid artery or to incomplete development of the tracheal ring following the long-standing external pressure that had existed throughout the life of the patient.

During the final week of observation on the ward, the patient's general condition was entirely satisfactory. The respirations were barely audible, but the patient appeared contented and playful and was completely free of any respiratory embarrassment.

Summary and Conclusions

The case is reported of an infant who was proved to have tracheal compression from a vascular ring within the mediastinum. The tracheal obstruction was particularly troublesome because of repeated attacks of superimposed tracheitis, for which the patient was hospitalized on four different occasions. Roentgenologic studies showed evidence of a vascular ring, and at operation the vessels were suitably divided to allow sufficient room for the trachea. The patient tolerated this surgical procedure extremely well and has had marked alleviation of symptoms.

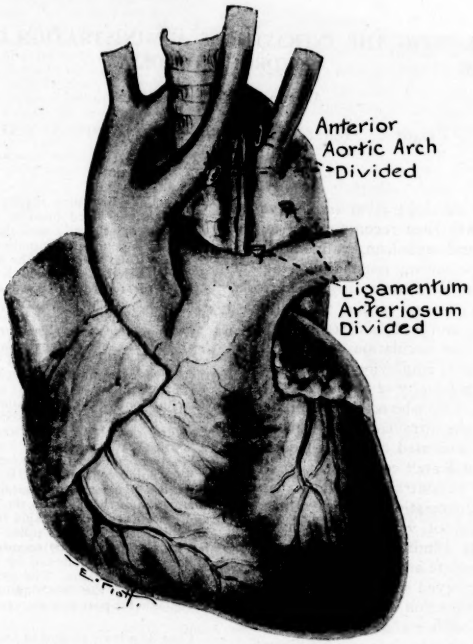

FIGURE 3. *Surgical Procedure.*

The ligamentum arteriosum was divided to allow the pulmonary artery to displace forward. The anterior arch of the aorta was divided to relieve compression of the trachea.

The detection of a vascular ring is apparently not difficult. Since in the vast majority of these patients some portion of the vascular ring passes behind the esophagus, fluoroscopic observation after a swallow of barium should show indentation of the posterior wall of the esophagus. If such esophageal deformity is found, the trachea can be studied by the introduction of lipiodol and by appropriate film studies in the anteroposterior and the lateral views, to detect any constriction of the trachea that may exist. Vascular rings do not always give rise to important clinical symptoms, but when the compression of the trachea is great enough to give rise to respiratory distress, surgical division of some portion of the ring should offer an excellent chance for relief of symptoms.

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DEATH FOLLOWING THE INTRAVENOUS ADMINISTRATION OF PAPAVERINE HYDROCHLORIDE*

A Report of Two Cases

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THE intravenous administration of papaverine hydrochloride has been recommended in the treatment of peripheral embolism, pulmonary embolism, mesenteric embolism, impending gangrene due to ergot, Raynaud's disease, angina pectoris, acute myocardial infarction, cardiac arrhythmias, renal and biliary colic and bronchial asthma and for the measurement of the circulation time.[1-12] Most discussions of its clinical employment stress its low toxicity and contain a paucity of warnings concerning possible dangers. Pal,[1] who originally advocated its use, implied that the intravenous administration might be dangerous and used only small doses by that route. Elek and Katz[11] concluded that intravenous injection may be contraindicated in complete auriculoventricular dissociation because they observed a short period of ventricular tachycardia following intravenous administration of the drug in a patient with complete heart block. Gray, Riseman and Stearns[12] observed severe reactions following the intravenous injection of papaverine hydrochloride in patients with coronary artery disease, and point out that the intravenous administration of drugs to such patients is not without danger.

We have recently encountered 2 deaths following the intravenous use of papaverine hydrochloride. Since a careful search of the literature has revealed no fatalities from this cause, these cases are being reported.

CASE 1. H. F., an 80-year-old man, collapsed because of weakness of the legs on the morning of admission to the hospital. The past history was negative except for prostatectomy 5 years previously, occasional edema of the ankles and slight dyspnea on exertion.

Physical examination revealed slight mental confusion, emphysematous but clear lungs and an enlarged heart with faint sounds, irregular rhythm and a loud apical systolic murmur. The blood pressure was 160/70. The peripheral vessels were sclerotic, and dorsalis pedis pulsations were absent. Two urine examinations were negative. Blood-cell counts, a blood smear and the nonprotein nitrogen level were normal. Blood Hinton and Kahn reactions were negative. An electrocardiogram showed auricular fibrillation, multiple ventricular ectopic beats arising from different foci, left-axis deviation, a diphasic T_1, an inverted T_3 and a normal Lead 4F.

Diagnoses of generalized arteriosclerosis, arteriosclerotic heart disease, auricular fibrillation, pulmonary emphysema and possible cerebral embolism were made. The only medications given were tincture of digitalis and chloral hydrate.

On the 4th day, the patient complained of pain in the legs. Examination revealed no change in physical or mental status except for the limbs, which showed paralysis, decreased temperature, absent pulsations and areas of blotchy livid discoloration extending up to 3 cm. below the umbilicus. A diagnosis of embolus to the bifurcation of the aorta was made.

Two cubic centimeters (0.065 gm.) of papaverine hydrochloride was given intravenously. Thirty to 40 seconds after completion of the injection the face suddenly became flushed and there was deep and rapid respiration for 1 minute. During this period the eyes rolled up and to the left, the head fell back, and the heart sounds were inaudible. The period of tachypnea was followed by apnea interrupted by several deep gasping breaths. The patient was pronounced dead 5 minutes after the injection of papaverine hydrochloride. Permission for post-mortem examination was not obtained.

CASE 2 (private patient of Dr. Nathan T. Bresnick). E. G., a 61-year-old woman, was admitted because of epigastric pain, fever and chills occurring 3 weeks after low amputation of the left thigh. Similar symptoms lasting for 24 hours had occurred the day following the amputation. The past history was negative except for diabetes mellitus for 11 years.

Physical examination revealed a rectal temperature of 103°F., a blood pressure of 138/92, an enlarged heart with a soft systolic murmur heard all over the precordium, dullness and fine crackling rales at both lung bases and pitting edema of the right leg. Urine examination was negative except for slight albuminuria and a few white cells in the sediment. The red-cell count was 3,350,000, the hemoglobin 68 per cent (Sahli), the white-cell count 16,650, and the fasting blood-sugar 205 mg. per 100 cc. An electrocardiogram showed normal rhythm, left-axis deviation, a small Q_2, a prominent Q_3, diphasic T_1 and T_2 and inverted T_3 and T_4 (Lead 4F).

The diagnosis of pulmonary embolism with infarct of the right lower lobe of the lung was made. Penicillin therapy was instituted, and on the 2nd day bilateral ligations of the femoral vein were performed. During the next few days the temperature fell to normal. Starting on the 5th day, however, the patient had episodes of sweating, weakness, dyspnea and apprehension and a pressing sensation in the anterior

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region of the chest. Examination during these periods showed dyspnea and rales throughout both lungs. It was thought that these episodes represented paroxysmal pulmonary edema occurring with or precipitated by angina pectoris or pulmonary emboli.

On the 10th day, during one of these episodes, the patient was given oxygen and a subcutaneous injection of 0.015 gm. of morphine sulfate and 0.0005 gm. of atropine sulfate. There was only slight relief of symptoms in 15 minutes, and an intravenous injection of 1 cc. (0.03 gm.) of papaverine hydrochloride was given. Thirty seconds later the patient took several deep breaths in rapid succession, followed by a period of apnea. The heart sounds were inaudible. During the next 2 or 3 minutes artificial respiration was carried out and 2 cc. of Coramine and 1 cc. of epinephrine hydrochloride (1:1000,) were given intravenously. Except for a few gasping breaths, however, neither respiration nor heart action could be restored, and the patient was pronounced dead 5 minutes after the intravenous injection of papaverine hydrochloride.

Autopsy. There was 200 cc. of serous fluid in both pleural cavities; the major branch of the pulmonary artery leading to the right lower lobe of the lung contained an adherent thrombus, and there was a recent infarct in this lobe. The heart showed no evidence of myocardial infarction, but there was an old occlusion of the right coronary artery and several points of narrowing in both major coronary arteries. Otherwise the examination was essentially negative.

Discussion

Previous reports have shown that untoward reactions may occur after the intravenous injection of papaverine hydrochloride. In animals, excitement, cardiac arrhythmias, respiratory distress and death, occurring with convulsions, ventricular fibrillation or respiratory arrest, have been described following administration of large doses.[13–19] In man, cardiac arrhythmias, respiratory disturbances and vasomotor reactions have been observed after the intravenous injection of therapeutic doses (0.03 to 0.13 gm.).[6, 10–12] The respiratory changes have been frequently noted and are described by Elek and Solarz[10] as the end point for the measurement of the circulation time. In most cases the symptoms experienced are not severe and are well tolerated. Gray, Riseman and Stearns,[12] however, mention several patients in whom severe reactions were encountered.

In the 2 cases reported herein death occurred following hyperpnea and tachypnea, which became manifest approximately thirty seconds after completion of the injection. Initially these abnormal respirations were similar to those frequently observed following intravenous administration of the drug. In the present cases, however, they marked the cessation of normal respiratory rhythm, being followed by apnea and a series of terminal gasping breaths. The heart sounds were not audible after the onset of respiratory symptoms, and death may have occurred as the result of either a cardiac or a respiratory disturbance. The mode of death was apparently an extension of the reactions generally encountered after the intravenous administration of papaverine hydrochloride.

In the cases described, death occurred within five minutes of the intravenous injection of papaverine hydrochloride, the duration of injection ranging from thirty seconds to one minute. Both patients were acutely ill at the time of injection but not moribund, and there was an abrupt unexpected change in their condition approximately half a minute after the injection. The chronological sequence and the symptoms observed suggest that the sudden death was related to the administration of the drug.

Summary and Conclusions

The intravenous administration of papaverine hydrochloride has been advocated in the treatment of a variety of conditions, in some of which its value is questionable. Although reactions have been observed following its intravenous use in man, most authors believe that there is little if any contraindication to its use by that route. The 2 cases reported herein show that the toxicity of papaverine hydrochloride is not so low as has previously been believed, for intravenous administration is apparently capable of causing death.

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RHEUMATOID ARTHRITIS: ITS VARIED CLINICAL MANIFESTATIONS*

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ONE of the greatest difficulties in recognizing rheumatoid arthritis, except in a severe, advanced form, arises from the fact that the disease may have many types of onset and may vary greatly in its course.[1–6] It often resembles other types of joint disease so closely that incorrect diagnoses are made and proper therapy is not instituted at a time when it is most beneficial.

The typical picture of rheumatoid arthritis is well known in its fully developed form.[1–9] Unfortunately, it is the severe, crippling stage that most physicians and patients visualize when the word "arthritis" is mentioned. Even in these typical cases, however, the early stages are not well recognized. Often prodromal symptoms of fatigability, anorexia, weight loss, and numbness and tingling in the extremities, with or without vague muscle and joint aching, precede joint manifestations by many months or years. Precipitating factors, such as physical or emotional strain, infections and accidental or operative trauma, often appear to play a role both in the initiation of the prodromal symptoms and in the production of articular manifestations of the disease. Characteristically in severe cases, the constitutional symptoms steadily increase and there is progressive, symmetrical involvement of many joints. The articular changes consist of pain, tenderness, swelling, — often with effusion, — thickening of periarticular tissues and limitation of motion with increasing deformities. Vasomotor symptoms, chiefly manifested by cold, moist hands and feet, are prominent in at least two thirds of the cases. Numbness and paresthesias in the extremities are of common occurrence. In severe cases, extreme atrophy of skin, muscles and bones occurs. The involvement of many nonarticular systems is made evident by the finding of anemia, lymphadenopathy, splenomegaly, subcutaneous nodules, iritis, pleurisy, pericarditis and myocarditis. The course in typical cases, even if untreated, is characterized by more or less complete remissions after varying periods of activity, often followed by subsequent exacerbations. In severe cases, the joints may show increasing residual damage after each exacerbation. Treatment, which will be discussed later, appears to hasten remissions and possibly prevent exacerbations.

The many variations in the onset and course of rheumatoid arthritis can best be made apparent by the presentation of cases. A typical case of moderate severity will be described first, and this can be used as a basis of comparison for the other forms of the disease as manifested in the subsequent case reports.

CASE 1. A 49-year-old, unmarried waitress was admitted to the hospital on October 15, 1932, complaining of joint pains of 6 months' duration. Early in 1932 she noticed easy fatigability and frequently experienced numbness of the hands. In April, 1932, the right shoulder suddenly became stiff and painful. These symptoms subsided in 3 days, but 2 weeks later the left ankle became swollen, tender and painful. Subsequently the right knee, the 2nd and 3rd left metacarpophalangeal joints, the right wrist and the jaws were similarly affected. The patient noted nervousness and weakness and lost 15 pounds in weight. The hands and feet were frequently cold, numb and moist.

The past history was of importance because the patient had had many operations and infections. She had had pleurisy on several occasions, typhoid fever in 1896, appendectomy in 1913, tonsillectomy in 1914, bilateral radical antrum operations in 1920, cholecystectomy, hysterectomy and bilateral oophorectomy in 1923 and a right-sided mastoidectomy in 1927. She had always had frequent colds, and for many years there had been some discharge from the right ear.

Examination on admission revealed a poorly developed, undernourished woman. There was slight arteriosclerosis of the vessels of the fundi and tenderness over both antrums. A few coarse rales were heard at the base of the left lung. The liver and spleen were palpable. Joint examination showed limitation of jaw motion, slight stiffness of the neck and swelling and tenderness of all the metacarpophalangeal and midphalangeal joints, the left knee, the left ankle and the left metatarsophalangeal joints. The laboratory findings were normal except for a corrected erythrocyte sedimentation rate of 1.35 mm. per minute.§ X-ray examination showed atrophy of the bones around the involved joints and narrowing of some of the phalangeal joints. Tonsillar tabs were removed on October 28, 1932. The symptoms and joint changes increased during the first 4 weeks after admission but slowly subsided during the last 6 weeks in the hospital. Treatment consisted of bed rest, exercises, hot packs on involved joints, antral washes, aspirin and added vitamins.

Following discharge, the patient continued to improve and by May, 1933, was free of all symptoms except slight fatigability and slight pain in the left knee. On examination, however, there remained slight periarticular thickening of the midphalangeal joints of both hands and slight swelling of the left knee. She remained relatively well until October, 1933, about 1 month after she had returned to work, when there was recurrence of fatigability and of pain and swelling in both hands, wrists, knees, left ankle and left foot. These symptoms again slowly subsided, and the patient became symptom free in June, 1934. At that time the joints were normal except for slight swelling of the 2nd and 3rd midphalangeal joints of the right hand and slight tenderness of the metatarsophalangeal joints of both feet. The sedimentation rate, however, remained elevated.

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§The sedimentation rates reported in this paper were determined by the method of Rourke and Ernstene.[10] The upper limit of normal is 0.35 mm. per minute.

The patient felt well until December, 1934, when symptoms began to recur following a period of severe emotional strain occasioned by incompatibility with the people with whom she was living. This exacerbation was of somewhat shorter duration than the previous one, the symptoms and most of the signs having disappeared by May, 1935. Since that time she has continued to have exacerbations of varying severity and duration. The usual precipitating factors have been emotional strain and, less frequently, overactivity or respiratory infections. She has had frequent attacks of bronchitis, and chest x-ray films have shown evidence of bilateral bronchiectasis. During remissions she has been relatively free of symptoms and has been able to carry on moderate activity. There has been some tendency for increasing deformities of joints following the repeated exacerbations of the disease. The only abnormalities found on examination of the joints in June, 1945, however, were slight swelling of the metacarpophalangeal and midphalangeal joints of both hands; slight limitation of motion of the neck, both shoulders, the left wrist and the right knee; limitation of extension and flexion of the right wrist to 20°; and a flexion deformity of 20° in the left knee.

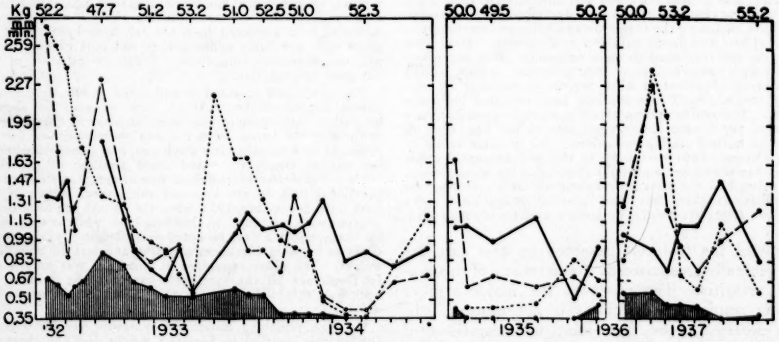

FIGURE 1. *Graphic Presentation of the Course of the Disease in Case 1 during the Period from 1932 to 1937. The solid line represents the sedimentation rate, the dotted line the subjective symptoms, and the broken line the objective joint findings. The hatched area represents that portion of the objective findings that is due to limitation of joint motion. In obtaining the subjective and objective figures, an arbitrary scale was employed assigning a value to each symptom and sign in each joint. The subjective symptoms include joint pain and stiffness, fatigue, malaise and general disability. The objective findings include the pain, swelling, tenderness and limitation of motion of the joints. The body weights are recorded at the top of the figure.*

This case demonstrates many of the characteristic features of rheumatoid arthritis. Prodromal symptoms were present for four months before any joint involvement was apparent. The latter was insidious in onset and then slowly progressive. The severity of the disease was indicated by the presence of x-ray changes in the bones as early as six months after the onset of joint symptoms. The role of emotional stress and other precipitating factors in initiating exacerbations of the disease is apparent.

The course of the disease between 1932 and 1937 is presented graphically in Figure 1. It is of significance that the sedimentation rate never returned to normal during remissions. A comparison of the sedimentation rate with the subjective and objective findings indicates that the rate reflected the clinical changes well during the early stages of the disease but subsequently became relatively fixed, changing very little during exacerbations and remissions.

In many cases of rheumatoid arthritis the onset and course vary greatly from those of the typical case described above and often duplicate those of other forms of joint disease. In the following case the sudden febrile onset after an acute infection, the skin rash and the migratory joint involvement with localization in a few joints led to a diagnosis of infectious arthritis. The subsequent course and findings made it apparent that the patient had rheumatoid arthritis.

CASE 2. A 38-year-old, unmarried music teacher was first admitted to the hospital on February 3, 1934, because of fever and painful joints of 4 weeks' duration. The family history revealed that her maternal grandmother had had generalized arthritis for many years. The past history was of significance only for the fact that at the age of 9 the patient had an attack of severe joint disease involving almost all the joints, and lasting 10 to 12 months. At the onset of this attack there was a high fever and redness and swelling of both knees and ankles. During 1933 she had been under severe emotional strain but had apparently been in good health until January 1, 1934, when after a thorough chilling she contracted a respiratory infection, with high fever, hoarseness and sore throat. The fever persisted and she noticed slight discomfort intermittently in various joints. Two weeks after the onset, both knees, the left hand and the left elbow became extremely painful, red and tender. Thereafter there were intermittent attacks of fever up to 105°F., and with each bout of fever there was exacerbation of joint pains.

On admission, the temperature was 105°F. The skin showed a few patchy areas of a slightly raised, erythematous rash. There was slight dullness, diminution of breath sounds and a few moist rales at the base of the right lung. Slight recession of the jaw was noted. The patient had considerable pain on moving. Both ankles and wrists and the midphalangeal joint of the right 4th finger were tender and red. The left knee contained a moderate-sized effusion.

Specimens of the urine showed an occasional trace of albumin and on several occasions contained many leukocytes. The white-cell count was 22,000 on admission and subse-

quently fell to 9000. The red-cell count rose from 3,400,000 to 4,300,000, and the hemoglobin from 50 to 85 per cent (Sahli). The corrected sedimentation rate varied from 1.00 to 1.50 mm. per minute. Blood and urine cultures were negative. Synovial fluid aspirated from the left knee showed a white-cell count of 9500, with 90 per cent polymorphonuclear leukocytes.

For 8 weeks the patient ran a spiking temperature with swings from 98.6 to 104 or 105°F., except for periods of 2 or 3 days during which the temperature remained around 100°F.

Tonsillectomy and adenoidectomy were performed 9 weeks after admission, at the end of this febrile period, without obvious effect on the course of the disease. Blood transfusions were given on two occasions. The right pleural cavity was tapped on April 25 and a few cubic centimeters of clear, yellow fluid containing 810 mononuclear cells per cubic millimeter was obtained. During the first 3 months of illness the patient lost 30 pounds, but regained 20 pounds before discharge. At the time of discharge in June, 1934, slight fatigability persisted, but all joint symptoms except migratory aches had subsided. Examination of the chest showed the same signs as at entry. The joints were normal.

During the 6 months following discharge all symptoms disappeared, and the sedimentation rate fell to 0.5 mm. per minute. The patient remained well until March, 1936, when she had a severe sore throat and developed pain in almost all joints, including the temporomandibular and sternoclavicular. These symptoms subsided in 2 months. Since that time she has continued to have occasional aches in various joints, with exacerbations of joint pain and swelling during respiratory infections or after periods of physical or emotional strain. Such exacerbations have persisted for many weeks. The sedimentation rate has risen to approximately 1.0 mm. per minute during these attacks but has fallen almost to normal during remissions. X-ray films taken in 1943 showed slight narrowing of the midphalangeal joints of the hands and feet and slight atrophy of the bones around the wrists and the metatarsophalangeal joints. During the exacerbations there has been marked fatigability. The involved joints are painful on motion and are often swollen.

Many of the features presented by this case are not generally recognized as characteristic of rheumatoid arthritis. The onset of the major attacks during respiratory infections is not unusual. In our experience the first joint manifestations of rheumatoid arthritis have been precipitated by infection in at least 20 per cent of the cases. Daily elevation of the temperature to 105°F., comparable to that seen in this case, may persist for more than a year in rheumatoid arthritis. Skin lesions resembling rashes of many types often appear during the active stage. The occurrence of pleurisy with effusion is less frequent but is occasionally observed. The similarity of the attacks that occurred at the ages of nine and thirty-eight is striking. It is probable that involvement of the temporomandibular joints in the first attack led to the recession of the jaw that was apparent at the time of admission to the hospital twenty-nine years later. In fact, the story of the childhood illness was obtained only on direct questioning after the observation of the jaw recession had suggested the probability that such an attack had occurred. The long remission between the attacks is not unusual.

The resemblance of rheumatoid arthritis to infectious arthritis is frequently seen in less severe cases than the above. In the following case, the sudden onset of joint symptoms and the exquisite pain and tenderness in the severely involved joints suggested the possibility of infectious arthritis, presumably gonococcal. The laboratory studies and the subsequent course failed to corroborate such a diagnosis and demonstrated that the patient had rheumatoid arthritis.

CASE 3. A 28-year-old machinist was admitted to the hospital on October 24, 1935, because of pain and swelling of the knees of 5 weeks' duration. The past history was not significant except for an attack of pain and stiffness in the left knee in 1931. Six weeks before admission the patient had an upper respiratory infection, and 1 week later developed pain in the temporomandibular joints. Three days later the pain in the jaws disappeared but the right knee became swollen and painful. Four weeks later the left knee and left shoulder became involved.

At the time of admission the temperature was 102°F. The general examination was negative. Both knees contained effusions and were tender. The right knee and hip could not be moved because of severe pain. A few days later the left wrist became swollen, hot and tender. The blood-cell counts were normal and urine examinations were negative. The corrected sedimentation rate was 1.88 mm. per minute. A gonococcal complement-fixation test gave a negative reaction, and prostatic smears showed no gonococci. Synovial fluid aspirated from the left knee contained 6300 white cells per cubic millimeter, 63 per cent of which were polymorphonuclear leukocytes. X-ray examination of the left knee was negative.

The symptoms subsided steadily, and at the time of discharge on November 23, 1935, joint examination showed only slight thickening of the tissues around the knees. Some stiffness of the knees, left wrist and neck continued for approximately 4 months after discharge, and during this period the patient frequently noted slight swelling of the right ankle. Thereafter he remained free of symptoms except for occasional pain in the knees or the lumbar region of the back until September, 1938, when the pain in the back began to recur each morning. In October, 1938, while sawing wood for many hours a day, he noted easy fatigability, developed slight stiffness in his knees and feet and lost 10 pounds in weight. The chest expansion at this time was only 4 cm. In December all the symptoms except slight pain in the back had subsided, although the patient continued to lose weight.

He then remained essentially symptom free for 6 years. During this interval he regained weight and the chest expansion increased to 9 cm. In 1943 his hours of work increased to 60 or 70 a week. There was no associated change in symptoms, but the sedimentation rate became elevated in October, 1943, for the first time in 6 years and the patient began to lose weight. One year later, following an upper respiratory infection in September, 1944, he had an exacerbation of his disease, with loss of weight and fatigability, as well as pain, stiffness and slight swelling in the metacarpophalangeal and midphalangeal joints of both hands and pain in the lumbar region of the back. With increased rest in bed and a reduction in the hours of work, the majority of the symptoms subsided within a month, although slight fatigability has continued.

The course of the arthritis in this case is presented in graphic form in Figure 2. It offers an interesting contrast to that of Case 1 (Fig. 1). In general, the sedimentation rate reflected the clinical course. It is noteworthy, however, that the rate did not return to normal for many months after the subjective and other objective evidences of disease had disappeared. Furthermore, the rise of the sedimentation rate in the last exacerbation preceded the clinical manifestations by many months. A fall of the rate to normal during remissions in general suggests a good prognosis, as in this patient, whose disease has remained in remission except on two occasions when exacerbations were precipitated by overwork.

Not infrequently, as exemplified by Case 4, the onset of rheumatoid arthritis resembles that of rheumatic fever and final diagnosis often cannot be made until the patient has been followed for many months.

Case 4. An 8-year-old girl was admitted to the hospital on February 24, 1942, because of joint pains and swelling of 9 months' duration. She had been perfectly well until September, 1939, when she had an acute sore throat. Three weeks later she developed high fever and migratory arthritis involving both ankles, knees and elbows and the temporomandibular joints. Two weeks after the onset of joint symptoms there was evidence of myocarditis and pericarditis. The patient was treated in another hospital and remained extremely ill for 8 months. Thereafter she improved steadily and apparently had no residual evidence of cardiac or joint damage. In October, 1940, a tonsillectomy was performed.

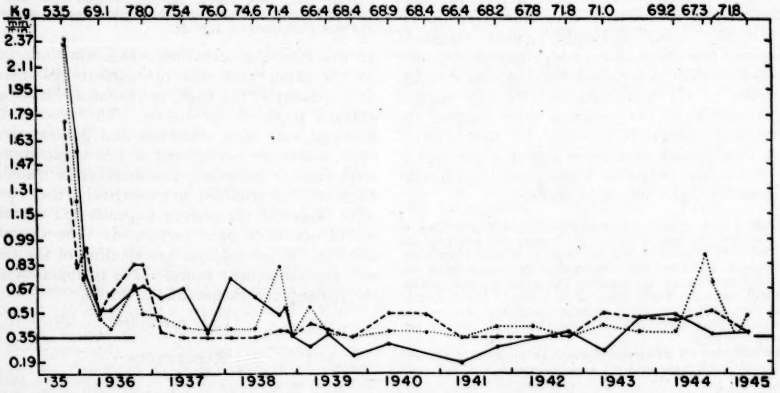

Figure 2. *Graphic Presentation of the Course of the Disease in Case 3.*

The solid line represents the sedimentation rate, the dotted line the subjective symptoms, and the broken line the objective joint findings. The method of obtaining the subjective and objective figures was the same as that used for Figure 1. The heavy line at 0.35 mm. per minute indicates the upper limit of normal for the sedimentation rate and forms the zero line for the subjective and objective findings. The body weights are recorded at the top of the figure.

She remained well, although on limited activity, until May, 1941, when she had recurrence of high fever, pain and swelling of many joints, especially the wrists and fingers, together with chest pain, dyspnea and orthopnea.

In July, 1941, the patient was admitted to another hospital. The only cardiac findings of significance were slight enlargement, a soft systolic murmur at the apex and a low T_1 in the electrocardiogram. There was no evidence of failure. She improved slowly and by November, 1941, the temperature had become normal, the corrected sedimentation rate began to fall from the original level of 1.5 mm. per minute and she began to gain weight.

At the time of transfer to this hospital there was slight cardiac enlargement, but no murmurs were heard. Joint examination showed slight recession of the jaw and slight limitation of motion of the neck, shoulders and elbows. The periarticular tissues of both wrists were thickened, and motion on the right was limited to 5° of extension and 10° of flexion. The metatarsal heads were depressed and there was a cockup deformity of the toes. Routine laboratory examinations were normal except for a sedimentation rate of 0.5 mm. per minute and a white-cell count of 19,000. There was x-ray evidence of slight cardiac enlargement to the right and left and dilatation of the left auricle. The wrists showed generalized decalcification of the bones, with several circumscribed areas of decreased density, and there was slight narrowing and irregularity of the joint spaces. The electrocardiogram was normal.

The patient continued to improve and at discharge on March 31, 1942, was free of symptoms. Motions of the joints had improved. The sedimentation rate remained elevated but had fallen to normal 1 month later. The patient returned to school in September, 1942, and has remained free of symptoms ever since. The sedimentation rate has remained normal except for an elevation to 0.5 mm. per minute on two occasions. The only residual changes in the joints are slight limitation of motion of both wrists and slight recession of the jaw. The heart is normal.

The acute onset three weeks after a sore throat, the migratory joint symptoms with relatively little swelling, redness or tenderness in the first attack and the involvement of the myocardium and pericardium were suggestive of rheumatic fever. The subsequent chronic involvement of joints with thickening of periarticular tissues and deformities and the x-ray evidence of decalcification of the bones around the joints and slight narrowing and irregularity of the articular spaces made it apparent that the correct diagnosis was rheumatoid arthritis. The high, spiking temperature, the extremely severe constitutional symptoms and the myocarditis and pericarditis are frequent manifestations of severe rheumatoid arthritis. During the first three years the disease remained active, although the partial remission for ten months gave evidence of the characteristic tendency to remit. Subsequently there was a complete remission, which has persisted through the past three years. Despite the severity of the disease, there are no residual joint findings except slight limitation of motion of the wrists and slight recession of the jaw, and there is no evidence

of cardiac abnormality. Slight retardation of growth often found in children with rheumatoid arthritis is apparent.

When the onset is monarticular, rheumatoid arthritis may resemble traumatic arthritis. Not uncommonly trauma is the precipitating factor that initiates the apparent onset of rheumatoid arthritis. In such cases attention is often focused on the injury, and to it is ascribed the subsequent joint involvement. If, however, joint symptoms do not appear for twelve hours or more after the injury or persist for months after uncomplicated trauma, one should hesitate to make a diagnosis of traumatic arthritis. In some cases evidence of involvement of other joints may be obtained by direct questioning as to each joint. Loss of weight, excessive fatigability or an increase in vasomotor symptoms constitutes further evidence against traumatic arthritis. Marked thickening of periarticular tissues, roentgenologic evidence of subchondral bone atrophy, elevation of the sedimentation rate and marked abnormalities in the synovial fluid suggest the presence of rheumatoid arthritis. In other patients, as in Case 5, such evidence is absent or overlooked and the correct diagnosis is not made until further progression of the disease has occurred.

CASE 5. A 23-year-old schoolteacher was admitted to the hospital on August 10, 1939, because of swelling and limitation of motion of the left knee of 1 year's duration. In August, 1938, her left knee locked in flexion when she squatted to pick up an object. The knee became swollen and stiff and only slowly returned to normal. Eight months later the swelling recurred without associated trauma and persisted to the time of admission. The past history was noncontributory.

Examination on admission showed an effusion in the left knee and tenderness in both tibiofemoral fossae and over the medial side of the joint. Routine blood and urine examinations were normal except for a white-cell count of 11,500 per cu. mm.

A diagnosis of internal derangement of the knee was made, and operation was performed on August 12. The synovial membrane was found to be thickened, and there was definite pannus formation in the region of the intercondylar notch. The cartilaginous surfaces of the joint seemed normal except in areas in which they were covered by pannus. The internal semilunar cartilage was hypermobile and was removed. Fluid aspirated at the time of operation contained 25,600 white cells per cubic millimeter, of which 96 per cent were polymorphonuclear leukocytes. The sugar content was 41 mg. per 100 cc. Microscopic examination of synovial tissue removed at operation showed a chronic synovitis consistent with that found in rheumatoid arthritis. There were hypertrophy and villous overgrowth of the synovial tissue. In the subsynovial layers there was widespread marked cellular infiltration consisting chiefly of mononuclear cells.

Following the operation the left knee remained swollen and stiff. In November, 1939, the patient noticed increasing fatigability and the left ankle and foot became swollen and extremely painful. In December, the right knee, right hip and right ankle became involved. The fatigability and weakness persisted, and early in 1940 there was involvement of the neck, left shoulder, left elbow, both wrists and the first and second metacarpophalangeal joints bilaterally.

The patient was readmitted on June 21, 1940. On direct questioning she recalled that she had been fatigued and had lost 10 pounds during the winter of 1938–1939, when she had been under physical and emotional strain. On admission she was emaciated and had marked atrophy of muscles, especially around the left shoulder girdle. The 1st metacarpophalangeal and interphalangeal joints of both hands were red, swollen and painful. There were limitation of motion and swelling of both wrists and both knees and only a few degrees of motion of the left shoulder in any direction. Routine blood and urine examinations were not remarkable. The corrected sedimentation rate was 0.78 mm. per minute.

On a regime of bed rest, exercises, hot packs to the left shoulder and both knees, aspirin, phenobarbital and discussion of emotional problems the patient steadily improved. She was discharged on July 24.

In this case, the operation, which was undertaken on the assumption that the patient had internal derangement of the knee, precipitated a more generalized stage of the disease. The synovial-fluid findings, with high white-cell and polymorphonuclear leukocyte counts and a low sugar content, were entirely inconsistent with those of traumatic effusions. If obtained preoperatively, they would have suggested the correct diagnosis and operation would not have been performed. The operative findings, the microscopic examination of the tissue and the subsequent course made it apparent that the patient had rheumatoid arthritis.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

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CASE 31461

PRESENTATION OF CASE

A forty-two-year-old woman entered the hospital in coma.

Five months before admission, in another hospital, she had undergone a right radical mastectomy for a malignant tumor. After the operation she received twenty courses of x-ray treatment over the operative site, the total dosage being 4800 r. The last irradiation had been given six weeks before admission. She felt well until several weeks before admission, when anorexia and gradually increasing weakness developed. At about the same time she began to complain of pain low in the back, which radiated down the right leg, with a sensation of numbness. Five days before admission she had a chill and vomited once. On the afternoon before admission, she developed a nonproductive hacking cough and a pink maculopapular rash broke out over the entire body. She became increasingly restless, and on the morning of the day of admission she was found in coma.

She had had spasticity of the right side of the body since birth. A chest film two months before admission showed clear lung fields with some coarsening of the markings.

Physical examination revealed the patient to be poorly nourished, cyanotic and in coma. The skin was hot and moist, and a rash consisting of papules with petechial centers was seen over the body, especially over the ankles and forearms. The eyes were wandering. The pupils were regular and equal and reacted to light. The mouth was opened with difficulty, and the pharynx was seen to be markedly injected. The neck was stiff but not more so than it usually was. A spastic palsy was present on the right side, with athetoid movements of the right hand, a right pes cavus and a dorsal scoliosis to the left. The right leg was shorter than the left. A right mastectomy scar was present. The skin was pigmented in this area. The heart was normal. The lungs were hyper-resonant, with tympany over the left upper lobe. There were no rales. The trachea was deviated to the left. The abdomen was normal. The reflexes could not be elicited.

*On leave of absence.

The temperature was 102°F., the pulse 140, and the respirations 32. The blood pressure was 108 systolic, 56 diastolic.

Examination of the blood showed a red-cell count of 3,580,000, with 8.9 gm.of hemoglobin. The white-cell count was 12,800, with 39 per cent neutrophils, 54 per cent lymphocytes and 7 per cent monocytes. The urine gave a ++ test for albumin, and the sediment contained frequent hyaline casts, a rare red cell and an occasional white cell.

A chest film taken with a portable machine soon after admission showed granular, diffuse areas of increased density, through which open bronchi could be traced, extending from each hilus outward to occupy the greater portion of each lung, apparently sparing only the lung tissue in the left lower chest and in the right apex (Fig. 1). There was no fluid in the pleural sinuses. The heart was somewhat enlarged. The hilar vessels could not be made out. Lumbar puncture revealed clear, colorless fluid under an initial pressure equivalent to 160 mm. of water; the cell count was 1 polymorphonuclear cell and no red cells per cubic millimeter; the total protein was 19 mg. per 100 cc. Blood and throat cultures were negative.

Twenty thousand units of penicillin was given every three hours intramuscularly. Later adrenocortical extract and 5 gm. of sodium sulfadiazine in 5 per cent dextrose in saline were administered. The patient's blood pressure fell steadily and she died twelve hours after admission.

DIFFERENTIAL DIAGNOSIS

DR. J. H. MEANS: One might say that this story separates itself into separate chapters. Five months before death this patient had a radical mastectomy for malignant disease of the breast, which I suppose was a carcinoma. Evidently they thought that it was a highly malignant one because they gave heavy radiation therapy after mastectomy. I do not know what interpretation to put on that with regard to whether or not the surgeon thought he got it all out. I gather that he did not think so. I asked one of our cancer experts about the policy here regarding radiation, and apparently there is a difference of opinion. Some men are inclined to give x-ray treatment in all such cases, whereas others do not do so unless they are quite apprehensive about recurrence, as for example when the axillary lymph nodes are involved. She did well for several weeks before admission, having apparently got through the mastectomy and heavy radiation therapy without much trouble. She then developed symptoms that consisted of anorexia and weakness, which are symptoms of so many things that one cannot interpret them. Then with the pain low in the back and the numbness in the right leg, one wonders whether she was developing metastatic disease in the spine.

The last chapter of this story seems to be an extremely acute affair, which began with a chill,

vomiting, a hacking cough and a maculopapular rash, which later became petechial. Her illness became productive of coma on the fifth day, and she died on the sixth day. It must have been an extremely fulminating infection.

Frankly, I find this a difficult problem, and I do not know what the answer is, but one has certain obvious lines of approach. In the first place, is there a possibility of explaining the whole picture on the basis of malignant disease? If possible, we like to explain the whole story on the basis of one diagnosis. Some people do have more than one disease though, and if one tries too hard to make everything fit one etiologic diagnosis one may come to grief. Except for a desire to connect the cancer with the terminal events, one would say that the terminal events were due to some sort of fulminating infection. There seems to be enough evidence suggesting infection to make one take that as one's first choice. Evidently the doctors in charge thought that infection might have been present, because they gave both penicillin and sulfadiazine, neither of which stopped the downhill course. What was the last illness characterized by? Chills and the onset of a rapidly progressive maculopapular rash. I did not see this rash, but I probably should not have known any more about how to interpret it if I had.

I cannot explain everything on the basis of cancer, but I can explain a number of things on that basis. Usually if one works hard to explain everything in the record, it turns out that some of the things are fakes. But I suppose the rash here described was really present. I wonder if a general carcinomatosis can produce a picture such as this, with cerebral, spinal and pulmonary metastatic disease. The fever is difficult to explain on the basis of cancer. The patient ended up in coma, also in shock. One wonders about that, and one notices that they gave adrenocortical extract. Did this patient's adrenal glands give out toward the end? They may well have, but there are various ways in which they may fail. They may fail in an infection of an overwhelming sort. I toyed with the remote possibility of involvement of both adrenal glands in a metastatic malignant process. I do not believe that this occurred, but it should be mentioned in an elaborate

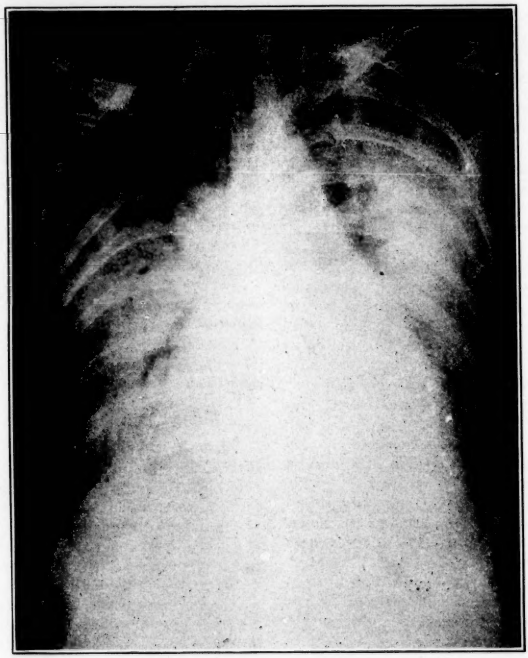

FIGURE 1. *Roentgenogram of Chest.*

differential diagnosis. I shall not say any more about the possibilities of malignancy because I really think that the patient had a superimposed terminal infection.

Another possible line of thought is that a non-malignant cerebral accident put her into coma. One has to think of all the possible causes of coma. This patient was never uremic, so far as I can make out on the data presented. One does not know the non-protein nitrogen, however. Was it done?

DR. HELEN S. PITTMAN: No; everyone thought that someone else had taken it.

DR. MEANS: Probably some kind of nephritis was found, but that is not the important picture. Nothing is said about the smell of the breath or anything of that sort, and I hesitate to make a diagnosis of uremia. She was not diabetic. She had not had a head injury. I do not believe that a cerebral accident would produce a fever of this sort. Embolus to the brain, cerebral hemorrhage, cerebral infarction and encephalitis do not seem to fit. There is no evidence of meningitis. The lumbar puncture was negative, and the neck was not stiffer than it always had been. Nothing is said about a Kernig sign. I cannot make a diagnosis of any kind of meningitis, although the rash may have been due to a meningococcal infection, which can produce a rash of this kind. I cannot go any farther with the intracranial situation or the causes of coma. I do recall that Dr. Stanley Cobb once pointed out that if a cerebral lesion is not productive of many symptoms and then an infection is superimposed, you could get all sorts of bizarre symptomatology. If she had something noninfectious in the head and then got an overwhelming infection, it might have produced this rapid development of coma.

Let us now work on the infectious part of the story. We have a little evidence pointing to the lung. The physical signs in the chest were queer. Of course, we should clear up the old business of birth injury, which comes in to confuse the picture with regard to the neurologic examination. I gather that she had old birth palsy, with shortening of the right leg and scoliosis. I wonder whether the deviation of the trachea had anything to do with the deformity of the chest. I shall call on the radiologist for help in a moment. Once in a great while one learns more by physical findings than the radiologist does by his technic, but that is unusual. Now these lung signs, — the hyper-resonance all over, the tympany in the left upper lobe, the absence of rales, the deviation of the trachea to the left and the loud harsh breath sounds, — about all I can get out of them is that it seems as if something was going on in the left upper lobe. Of course the deviation of the trachea makes one think that there was something pushing or pulling it over. If it was being pulled over, one would think of collapse, but if the lung was collapsed, I do not believe that one would expect to get harsh breathing. It is possible, I suppose, if the bronchus was open. I shall reserve final opinion on that until I have seen what the radiologist can do for me.

DR. CLAYTON H. HALE: It is difficult to explain the hyper-resonance in the chest from these films. I presume that there might have been some at the extreme right apex.

DR. MEANS: The tympany was at the left apex, over the left upper lobe, and that portion of the film is duller than the other. It does not make sense.

DR. HALE: I believe that there is some aeration, at least in the left lower lobe. I can see part of the left half of the diaphragm laterally, but the heart shadow obscures the remainder. This is a diffuse granular density. The upper and lower lobe bronchi on the right are demonstrated quite nicely, and thus we know that they are open. Here you can see a small horizontal shadow that appears to be the upper border of the middle lobe. Separating this from the density above suggests a circumscribed shadow that might be a metastatic mass in the right upper lobe. The trachea is in normal position. The heart looks large on these films, but they were made with a portable machine. I believe that one has to think of malignant disease and possibly superimposed consolidation in the other areas. I should not expect pulmonary edema to give a sharply demarcated area like this. I see no evidence of metastases to the bones and no collapse of any of the lobes.

DR. MEANS: There was no collapse, and no fluid in the chest. We can forget the deviation of the trachea for the present. I must confess that by the x-ray studies I am more intrigued with my interpretation that a good deal of this picture might have been due to cancer than I was before I saw the films. It could have been a metastatic malignant lesion in the chest, and if it was in the chest it might also have been in the head. I think that I shall rest my case on a statement something like the following. The patient originally had a carcinoma of the breast, and she then developed the picture of rather widespread metastatic carcinoma. There is no x-ray evidence that it involved the spine. Is that an adequate roentgenologic study to exclude the spine?

DR. HALE: No.

DR. MEANS: Then I do not know whether or not she had it in the spine, but the history suggests that she may have. She had it in the lung and probably in the brain. I think that she had an old cerebral lesion, presumably due to birth injury, and that might turn up in the way of anything that the pathologist can find. She may have had a terminal infection of some sort. It could have been an overwhelming meningococcal infection or, of course, a streptococcal infection. I wonder if she could have had a rapidly progressing subacute endocarditis. She may have, but I do not see how one can make the diagnosis. I am simply going to let it go as a terminal infection of some kind. There may have

been a pneumonitis mixed up with this picture, but how much of the pulmonary lesion was due to pneumonitis and how much to cancer, I cannot say. I shall have to let it go at that.

DR. PITTMAN: I am glad that Dr. Means could not make a diagnosis either. Dr. E. L. Young operated; because of the spasticity from the birth injury he was unable to abduct the arm sufficiently to get at the field, and he thought that he had not done an adequate axillary dissection. For this reason, extensive irradiation was given.

DR. MEANS: Speaking of irradiation, I thought of the possibility of pulmonary fibrosis resulting from irradiation, but that would only be directly under the operative site and would not explain such a widespread lung lesion.

DR. PITTMAN: She had this episode of chills and vomiting, and five days later, when she was found unconscious, Dr. Young was called. He made a diagnosis of intracranial metastases and had her sent to Dr. W. J. Mixter. When Dr. Mixter obtained normal spinal fluid under normal pressure, he decided that there was nothing in the head and asked me to see her. At that time she had quite an insignificant skin rash, but it progressed rapidly during the course of the afternoon. She entered the hospital with signs that I interpreted clinically as indicative of spontaneous pneumothorax. She then developed pulmonary edema. Dr. Gardella, the resident, suggested that she had a meningococcemia, with the Waterhouse–Friderichsen syndrome. I had not thought of that, but it seemed a reasonable diagnosis. Dr. Mixter, who had seen a number of cases in World War I, agreed, and from that point on the problem was therapeutic. She came out of the pulmonary edema but nevertheless went into shock. She was obviously moribund before getting what was, perhaps, overzealous therapy.

DR. MEANS: I had not thought of the possibility of her dying because of so much intravenous therapy. Is that what you are implying?

DR. PITTMAN: She was dying anyway. The therapy may have produced the anatomic picture of pulmonary edema.

CLINICAL DIAGNOSIS

Meningitis.

DR. MEANS'S DIAGNOSES

Metastatic cancer of lungs, probably brain and possibly spine.
Terminal infection (type undetermined).

ANATOMICAL DIAGNOSES

Radiation pneumonitis.
Papular rash.
Scar: right mastectomy.

PATHOLOGICAL DISCUSSION

DR. RONALD C. SNIFFEN: At the time of death this patient showed the deformities described in the clinical history. There was a papular rash over all extremities, most pronounced on the flexor surfaces. A few papules were scattered over the anterior chest, and a few macules over the abdomen; no petechiae could be found. The right mastectomy wound was well healed, and there were no signs of local recurrence. There was slight tanning of the skin in this region. Each pleural cavity contained approximately 150 cc. of clear, straw-colored fluid, and each lung weighed 900 gm., which is about three times the normal weight. This increase in weight was largely accounted for by a profound pulmonary edema. There were no pleural adhesions or thickening. No other gross abnormalities were found. The heart was entirely negative. The adrenal glands merely showed medullary autolysis, no metastatic cancer being detected. A blood culture grew only colon bacilli.

The important microscopic findings were confined to the lungs, and they are of interest. In general there was a severe pulmonary edema, but all sections showed additional abnormalities. The cells lining the alveoli and atria had increased tremendously in size (Fig. 2). Many showed extreme hypertrophy and distortion and were gradually desquamating into the alveolar spaces; a few of these cells were multinucleated. Many of the alveoli contained a thick homogeneous hyaline membrane, which was closely applied to the alveolar wall or was slightly lifted from it. The alveolar walls were hyperemic and edematous, the endothelial and septal cells were swollen, and the elastic fibrils were thickened and fragmented.

No one of these pulmonary changes is peculiar to any one condition, but in this combination they are said to be characteristic of radiation pneumonitis. Warren and Gates[1, 2], and Warren and Spencer,[3] have reported these reactions in detail from a study of autopsy material and have produced them experimentally in various animals by means of radiation.

DR. MEANS: What was the round mass in the chest that the radiologist talked about?

DR. SNIFFEN: We did not find a mass. Severe pulmonary edema was the only gross abnormality.

DR. HALE: Were these microscopic changes present in the left lung?

DR. SNIFFEN: Unfortunately our sections were not taken with reference to the field of radiation, but all of them showed the same abnormalities and blocks of tissue were taken from each lung.

DR. CHARLES S. KUBIK: It is not often that we have a chance to observe the pathologic lesions of infantile hemiplegia so many years after its onset. The left cerebral hemisphere was considerably smaller than the right. The left cerebral peduncle was extremely small, owing to secondary degenera-

tion of the corticospinal tract. The original lesion was probably in the left lenticular nucleus and internal capsule; nearly all the lenticular nucleus was destroyed, and the degeneration of the corticospinal tract was unquestionably due to involvement of the internal capsule by the lesion. There was no residual softening, cavitation or discoloration but, so far as one could tell, only a loss of substance. The nature of the original lesion is not clear. I suppose that it was acquired, not developmental, and it may have resulted from a birth injury.

DR. MEANS: I feel reconciled about this case. Evidently even the pathologists do not know the cause of death.

DR. SNIFFEN: I believe that the radiation pneumonitis was the major contributing factor. We were unable to find evidence of a superimposed fulminating infection.

FIGURE 2. *Photomicrograph of Lung.*

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CASE 31462

PRESENTATION OF CASE

A fourteen-year-old boy entered the hospital complaining of pain in the right small toe.

Five months before admission the patient first noticed that walking or direct pressure to the toe caused sharp pain. Immersion in cold water also caused pain. There was no history of previous trauma. He was seen in the Out Patient Department three months before admission, where examination showed tenderness and redness but no limitation in motion. The impression was that the soft-tissue swelling was due to a tight shoe. He was seen in the Out Patient Department a few times during the next two months. X-ray studies showed an area of rarefaction involving the terminal phalanx of the right fifth toe. There was no definite periosteal proliferation. Soft-tissue swelling was considerable. Removal of the toe was advised.

On admission, physical examination was negative except for marked swelling of the right small toe, which was enlarged to twice its normal size. It was especially tender on the dorsal surface but not red or warm beneath the nail. A blister was present on the plantar aspect. Motion of the toe was limited.

Examination of the urine and blood was negative. A blood Hinton test was negative. The blood uric acid was 6.2 mg. per 100 cc. (normal).

X-ray films of the toe showed somewhat more decalcification of the terminal portion of the distal phalanx than was seen previously. The periosteal outline was preserved, and in the center of the decalcification there was a dense area (Fig. 1). An x-ray film of the spine was negative.

An operation was performed.

Differential Diagnosis

Dr. John Reidy: We might begin by looking at the x-ray films.

Dr. Clayton H. Hale: This film shows the soft-tissue swelling that was described and the decalcification of the distal half of the terminal phalanx. A film taken some two months later shows extension of the decalcification. I can make out no periosteal reaction. I cannot tell whether the soft-tissue swelling is arising from the phalanx or the surrounding soft tissue.

Figure 1. *Roentgenogram of Terminal Phalanx of Fifth Toe.*

Dr. Reidy: Is there anything circumscribed about it, or is it generalized decalcification?

Dr. Hale: It extends to the junction of the proximal and middle thirds, where there is a rather abrupt transition from normal to decalcified bone.

Dr. Reidy: It chiefly involves the terminal portion of the phalanx.

Dr. Hale: On this other film you can see the junction of the decalcified area with the supposedly normal bone, and I presume that this is the dense island described in the center of the decalcified area.

Dr. Reidy: What would you take the dense spot to be — new-bone formation or the remains of the old shaft?

Dr. Hale: It seems likelier that it represents the remains of the old shaft, but it is difficult to tell. It is surrounded by decalcified bone.

Dr. Reidy: In a fourteen-year-old boy with these symptoms one would consider first of all, as they did in the Out Patient Department, pressure due to tight shoes. If that had been the case, however, I am sure that he would have been relieved.

This apparently was a destructive type of lesion, yet there is no evidence of periosteal proliferation, which I believe is more or less against its being an infectious process, either of pyogenic or tuberculous origin. The negative laboratory studies, that is, those of the blood and the urine, are also against its being an inflammatory process. The fact that he had a blister on the plantar surface of the toe suggests that this might have been the point of entrance of an infection. Yet the blister was present five months after the onset of the original symptoms, so I doubt that it played any part in the primary process. It was likelier the result of the marked swelling rather than the cause of it. Tuberculosis or a low-grade inflammatory process should be considered. Yet, here again there should have been some evidence of regeneration of bone if it had gone on for this length of time, although probably less than what would have been present with a pyogenic type of infection. There is no mention of a tuberculin test. Apparently they were not considering this possibility. There is no evidence of tuberculosis elsewhere in the body, so I believe that tuberculosis was probably not the cause of the difficulty.

The fact that x-ray films were taken of the lumbar spine suggests a neurotrophic lesion, that is, something that had resulted from a spina bifida or a nerve-root irritation. This type of lesion is usually associated with an inflammatory reaction, and usually there is no pain. The facts that he had pain and no evidence of periosteal proliferation and that the x-ray films of the spine were negative make me believe that a neurotrophic disturbance was probably not responsible for his difficulty.

Gout should be thought of, since we know that it will produce lesions in the bones and joints. To have a single lesion in a fourteen-year-old boy would be most unusual. Furthermore, there is no other evidence of bone or joint difficulty, and the blood uric acid level was normal. Therefore I do not suspect gout too seriously.

The other things that one might consider are enchondroma of bone. This would probably give

a much more clear-cut picture than we have here. Although enchondroma does occur in the terminal phalanx it rarely ever causes pain unless there is a fracture through it. Do you think there is any evidence of this, Dr. Hale?

DR. HALE: I cannot see a fracture.

DR. REIDY: If the bone had been fractured, it would have healed fairly promptly and the symptoms would have been relieved. The same reasoning probably holds true for xanthoma or any kind of cystic bone disease. The symptoms are not since he continued to complain of it over this period of time. I believe that the picture best fits into the so-called "glomus-tumor" syndrome, a condition in which the tumor arises from the connecting mechanism between the terminal arteriole and primary venule and may cause bone destruction by direct pressure. This causes severe pain, and is not unusual in the subungular area. I have seen the thumb involved several times. I do not recall having seen one in the foot, but the character of the pain and the lack of any other diagnostic feature

FIGURE 2. *Photomicrograph of Nidus in Terminal Phalanx of Fifth Toe.*

marked unless something in the way of injury occurs. These conditions are susceptible to injury because of the weakened bone. A subungual exostosis can occasionally cause considerable discomfort, but it would not produce this type of picture, even with the atrophy of disuse that goes with it. If he had pain to that extent, there would be decalcification in the remaining toes, as well as in the terminal phalanx of the fifth toe. A so-called "subungual melanoma" might be considered, but in five months one certainly would expect much more evidence of destruction and complete discoloration and probably some breaking down of the tissues.

The type of pain is consistent with a neurovascular lesion. The pain was aggravated by changes in temperature and apparently was fairly severe, certainly suggest a glomus tumor as a good possibility. The only thing against a glomus tumor is the fact that there was no evidence of discoloration beneath the nail, which is usually present. I believe, however, that this fills the bill better than any other lesion that I can think of, and I shall make a diagnosis of glomus tumor of the terminal phalanx of the right fifth toe.

CLINICAL DIAGNOSIS

Glomus tumor of terminal phalanx of right fifth toe.

DR. REIDY'S DIAGNOSIS

Glomus tumor of terminal phalanx of right fifth toe.

Anatomical Diagnosis

Osteoid osteoma of terminal phalanx of right fifth toe.

Pathological Discussion

Dr. Ronald C. Sniffen: When the terminal phalanx was split longitudinally one could see an injected, firm, circumscribed area approximately 5 mm. in diameter in the distal tip. This nidus lay in the medulla and had not broken through the cortex.

Microscopically the nodule showed a background of vascular connective tissue in which trabeculae of osteoid were embedded, and these were lined by osteoblasts and, at some points, by osteoclasts. Occasionally the osteoid seemed to be undergoing calcification (Fig. 2). The trabeculae of the adjacent spongy bone were somewhat thickened.

There was no inflammatory infiltration in the bone, nor evidence of degeneration. Our diagnosis was osteoid osteoma. Apparently the small nidus had produced quite a severe reaction around it as a consequence of repeated trauma. This is the first osteoid osteoma we have seen in this region. Jaffe and Lichtenstein* have reported several cases in which the lesion arose in the pedal phalanges.

Dr. Hale, with the knowledge that this is an osteoid osteoma, can you see the nidus in the roentgenogram?

Dr. Hale: The 2-mm. area of increased bony density surrounded by decalcified bone probably represents the nidus of osteoid osteoma.

*Jaffe, H. L., and Lichtenstein, L. Osteoid-osteoma: further experience with this benign tumor of bone. *J. Bone & Joint Surg.* **22**:645-682, 1940.

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SAFE AND SANE FOURTH

Many thoughtful persons have come to the conclusion, in recent years, that war as a major calamity ranks second only to that greatest human calamity of all — man's inhumanity to man, of which war, after all, is only an organized expression. And yet nations that are, on the whole, peace loving so long as they can have their own way occasionally enter into war if the provocation or the danger that is pressing seems great enough.

To measure the losses and the gains after the deed is a chastening experience. The main goal may have been won, but goals are often illusive, and the cost is always excessive. It would be folly to attempt now to run a trial balance on the tangled affairs of the last four or five years; we can only say that we have saved ourselves from immediate oblivion, whatever the cost. Whether we can ever pay this immediate cost or, indeed, the continuing and mounting cost of man's inhumanity to man is another matter.

Aside from the main decisions that are now being contested among the winners themselves, some slight benefits may be checked against the losses in material, in lives and portions of lives and in moral values. There is no denying that technology has made great advances both in destruction and in its antidotes, and many of these discoveries can be directed toward peacetime uses. Even atomic energy, about which we are now becoming almost blasé, will revolutionize industry and life itself, they say, if life survives the experiment. Medicine and surgery, as always, gain impetus through the need of saving life and limb in time of war. For those that are tough enough not to be consumed by it, the crucible of war may be a refining agent, just as the experience of working in a common cause against a common danger is an uplifting one if its beneficiaries can overcome the demoralizing effect of release from that danger; labor gains in importance and earns higher rewards each time it becomes a partner in any important enterprise, and its benefits will become lasting in proportion to its ability to appreciate the mutuality of its partnership.

It was, however, the safe-and-sane Fourth of July on which we had planned to comment. Designed and enforced as a war measure to conserve ammunition and keep our powder dry, its continuance in the halcyon days of peace will signalize a real and revolutionary step in the progress of civilization. A race that has learned in time of war to respect the agents of destruction in times of peace has certainly something to add to the credit side of the ledger.

ALBRECHT DÜRER AND ANATOMY

Although Dürer is widely recognized as the father of copper-plate engraving for book illustrations and also as one of the great painters of his age, his work on anatomy, particularly in relation to the proportions of the human body, is less well known. He began to be interested in this subject early in his life. Apprenticed at the age of fifteen to Michael

Wohlgemuth, the foremost wood engraver of his day, Dürer had the best of training. After seven years he was sent by his father on an extended trip throughout Europe, and it was in Italy, just before the turn of the sixteenth century, that he caught the significance of picture printing in contrast to book printing, which by that time was firmly established, with the presses pouring out incunabula in considerable number. Dürer visualized the propagation of thought by the use of pictures, and since he was essentially an artist, he studied in particular the delineation of the human figure.

Returning to his native Nürnberg, he soon became intimate with such humanists as Hartmann Schedel and Willibald Pirkheimer, and it was during the years just after 1500 that Dürer made his great series of copper engravings, including *Melancholia*, so well known to physicians, as an expression of intellectual research. About 1528 he painted *The Four Apostles*, his highest achievement in art.

His book *On Human Proportions* occupied many years of his life but was not published until just after his death in 1528. The first edition, in German, contains superb engravings showing the surface anatomy, with particular attention to studies of the various proportions of the body. Dürer drew not only figures of persons of various size and shape but also infants and a few suffering from diseases that had deformed their stature. It is from this book that most subsequent studies in art anatomy have developed, and the illustrations, drawn so exquisitely by Dürer, are frequently reproduced in textbooks of the present day. Apparently the German edition of 1528 was not widely disseminated, for it was not until the book was translated into Latin, the language of the scholar, in 1532–1534 that Dürer's famous work became widely known. Additional translations into French, Italian, Portuguese and Dutch were made within a few years. The edition of 1528 is a rare book, and all the early publications are not by any means plentiful. Few men, by one publication, have exerted a wider influence.

MASSACHUSETTS MEDICAL SOCIETY
POSTWAR LOAN FUND

The Postwar Loan Fund has been set up, and all discharged medical officers who were members of the Massachusetts Medical Society in good standing at the time of their entry into the service may apply for loans from this fund. For further information apply to:

George L. Schadt, *Chairman*
Postwar Loan Fund
8 Fenway
Boston 15, Massachusetts

NOTICES

NEW ENGLAND HEART ASSOCIATION

A meeting of the New England Heart Association will be held in the Boston Medical Library on Monday, November 26, at 8:15 p.m.

PROGRAM

The Use of Cytochrome C in Combating Tissue Anoxia. Dr. Samuel Proger.

Testosterone Propionate Therapy in 100 Cases of Angina Pectoris. Dr. Maurice A. Lesser.

Surgical Treatment for Coarctation of the Aorta. Dr. Robert Gross.

Venous Catheterization in Patients with Congenital Heart Disease. Drs. C. Sidney Burwell and Lewis Dexter.

Experiences during the Past Year at the Massachusetts General Hospital in the Dietetic Treatment of Congestive Heart Failure. Drs. William C. Bridges, Edwin Wheeler and Paul D. White.

Interested physicians and medical students are cordially invited to attend.

SOUTH END MEDICAL CLUB

The next meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, November 20, at twelve noon. Dr. Thomas J. Anglem will speak on the subject "Thiouracil in the Treatment of Thyroid Disease." Dr. Frederick J. Simmonds will preside.

Physicians are cordially invited to attend.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 22

FRIDAY, NOVEMBER 23

*9:00–10:00 a.m. Some Aspects of Penicillin Therapy. Dr. Maxwell Finland. Joseph H. Pratt Diagnostic Hospital.

*9:00–10:00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.

10:50 a.m. Dermatophytosis. Dr. Ernst Bernhardt. (Postgraduate clinic in dermatology and syphilology.) Amphitheater, Dowling Building. Boston City Hospital.

SATURDAY, NOVEMBER 24

*10:00 a.m.–12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

MONDAY, NOVEMBER 26

*12:00 m.–1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

*8:15 p.m. New England Heart Association. Boston Medical Library.

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